INHIBITORS OF CYSTEINE PROTEASES AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S.S.N. 63/036,866 filed June 9, 2020; U.S.S.N. 63/039,297 filed June 15, 2020; U.S.S.N. 63/067,669 filed August 19, 2020; U.S.S.N. 63/091,630 filed October 14, 2020; U.S.S.N. 63/129,018 filed December 22, 2020; U.S.S.N. 63/171,675 filed April 7, 2021; U.S.S.N. 63/172,478 filed April 8, 2021; U.S.S.N. 63/173,146 filed April 9, 2021; U.S.S.N. 63/179,128, filed April 23, 2021; and U.S.S.N. 63/195,460, filed June 1, 2021; the contents of each of which are incorporated herein by reference in their entirety.

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. The ASCII copy, created on June 3, 2021, is named PARB-004WO_SL.txt and is 3,285 bytes in size.

BACKGROUND

[0003] The Coronaviridae family of viruses are enveloped, single-stranded, positive-sense RNA viruses and include 141 species classified into four genera according to their phylogenetic relationships: α-, β-, γ-, and δ-coronavirus. Coronaviruses (CoVs) are zoonotic viruses that infect a variety of animals from whales to birds, bats, cats, and humans. Typically, CoV infection results in mild to moderate respiratory tract infections; however, some CoV species are extremely virulent and can result in widespread fatality. Severe acute respiratory syndrome coronavirus (SARS-CoV) is a human CoV responsible for the first pandemic of the 21st century, infecting over 8,000 people with a 10% mortality rate. Middle East respiratory syndrome coronavirus (MERS-CoV) was identified in November 2012 and had since infected over 1,600 people in 26 countries with a 36% mortality rate. More recently, COVID-19 (SARS CoV2) coronaviruses have raised a global pandemic since they had been first identified in China in late 2019.

Therefore, it is important to identify coronavirus drug targets that can be utilized for the development of broad-spectrum anti-coronaviral therapeutics to combat infections of existing and emerging coronaviruses.

[0004] All CoVs express a >800 kDa replicase polyprotein that contains either two or three cysteine proteases, the papain-like protease(s) (PLPpro, or PLP1 and PLP2) and the 3C-like protease (3CLpro, nsp5, or Mpro). These proteases process the CoV replicase polyprotein by cleaving it into 16 non-structural proteins, which are responsible for a variety of aspects of CoV replication. The CoV 3CLpro is responsible for processing 11 cleavage sites within the replicase polyprotein and is essential for CoV replication, making it a highly valuable target for therapeutic development. The overall active site architecture and substrate recognition pockets are structurally conserved across CoV 3CLpros, increasing its attractiveness as a target for the development of broad-spectrum anti-CoV therapeutics. Moreover, high sequence conservation in the vicinity of the active site among CoV 3CLpros from different coronavirus subclasses make them an excellent target for the development of broad-spectrum therapeutics for coronavirus infections. Accordingly, the development of CoV 3CLpro inhibitors is a promising path for the treatment of respiratory tract infections and related diseases.

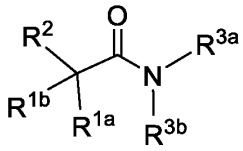
[0005] Numerous studies on targeting the immediate zoonotic reservoirs of coronaviruses with small molecule inhibitors have helped inform structure-based design strategies aimed at creating molecular scaffolds that may aid in the development of therapeutic against coronaviral infection; however, small molecule antiviral agents or effective commercially available broad-spectrum therapeutics have not yet been identified. There is a critical need for the development of broad-spectrum CoV therapeutics to overcome the challenges of traditional anti-CoV therapeutic development, as broad-spectrum therapeutics can be rapidly implemented upon zoonotic disease outbreak.

SUMMARY

[0006] The disclosure is directed to, in part, viral protease inhibitors. Also disclosed herein are pharmaceutical compositions comprising at least one disclosed compound and a pharmaceutically acceptable carrier.

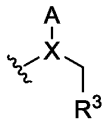
[0007] In an embodiment, disclosed herein is an antiviral compound, comprising a warhead covalently bound to a 3C or 3CL protease inhibitor, wherein the antiviral compound covalently binds to a Cys residue of the protease, and wherein the antiviral compound is active against one or more viruses.

[0008] Also disclosed herein are compounds represented by Formula II:



Formula II,

or a pharmaceutically acceptable salt, stereoisomer, ester, or prodrug thereof, wherein:

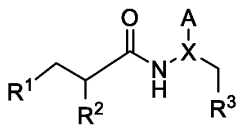
R^{3a} is selected from 

and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A; R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from C_6-C_{14}aryl and a warhead A; R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl; R^{1b} is selected from hydrogen and C_1-C_8alkyl; or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen, NR^G, or a C_3-C_{10}cycloalkyl; R^1 is selected from the group

consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A; R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, $-CH_2CF_3$, $-CF_3$, $-O-CF_3$, $-O-CHF_2$, $-S-CH_3$, $-S(O)_2-CH_3$, $-NH_2$, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, $-NHC(O)R^B$, $-NHC(O)OR^B$, $-NHC(O)O-(C_1-C_8alkyl)-R^B$, $-N(R^y)_2$, $-N(R^y)(C_1-C_8alkyl)C(O)O$-phenyl, $-N(R^y)(C_1-C_8alkyl)C(O)N(R^y)_2$, $-C(O)-OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, $-NH_2$, hydroxyl and oxo; R^2 is selected from the group consisting of $-NHC(O)R^B$, $-NHC(O)N(R^B)_2$, $-NHC(O)C(R^C)_2R^B$, $-NHS(O)_2R^B$, –O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x; or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered monocyclic or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A; R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A; R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{16}cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle; R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl; R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, $-O-(R^{xx})-OCH_3$, $-OCHF_2$, $-OCF_3$, –O-(C_1-C_8alkyl), $-C(O)O(CH_3)$, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, $-N(R^y)(C_1-C_8alkyl)C(O)N(R^y)_2$, $-N(R^y)(C_1-C_8alkyl)C(O)OH$, $-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, $-O-C_6-C_{14}$aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle; wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they

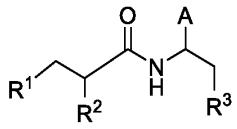
are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl; R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-C_{3-6}cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{ii}; R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m; R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy; R^{ii} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_1-C_6alkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2; R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo; R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6; R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH; A is a warhead; and X is selected from the group consisting of C(R^{xy}) and N, wherein R^{xy} is selected from the group consisting of H, D, -OH, -NH_2, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy.

[0009] In some embodiments, disclosed herein are compounds represented by Formula II-A:



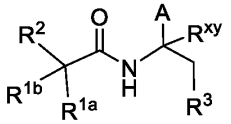
Formula II-A.

[00010] In some embodiments, disclosed herein are compounds represented by Formula II-B:



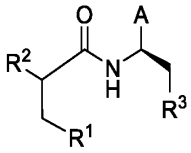
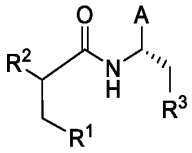
Formula II-B.

[00011] In some embodiments, disclosed herein are compounds represented by Formula II-C:

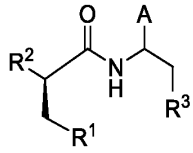
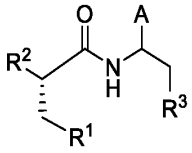


Formula II-C.

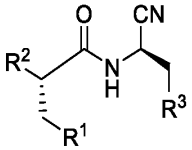
[00012] In some embodiments, disclosed herein are compounds represented by Formula II-D-A or Formula II-D-B:

 (Formula II-D-A) or  (Formula II-D-B).

[00013] In some embodiments, disclosed herein are compounds represented by Formula II-E-A or Formula II-E-B:

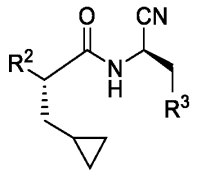
 (Formula II-E-A) or  (Formula II-E-B).

[00014] In some embodiments, disclosed herein are compounds represented by Formula II-F:



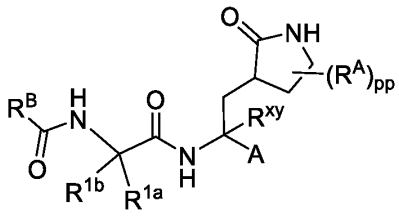
Formula II-F.

[00015] In some embodiments, disclosed herein are compounds represented by Formula II-G:

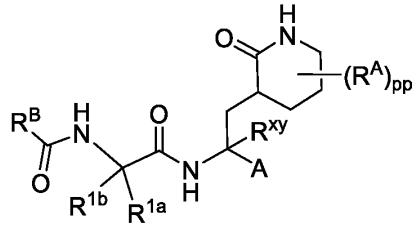


Formula II-G.

[00016] In some embodiments, disclosed herein are compounds represented by Formula II-H-A or Formula II-H-B:



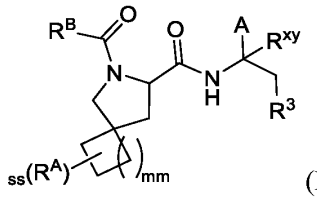
(Formula II-D-I), or



(Formula II-D-II),

wherein pp is selected from 0, 1, 2, and 3.

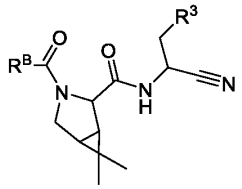
[00017] In some embodiments, disclosed herein are compounds represented by Formula II-E:



(Formula II-E),

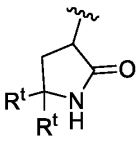
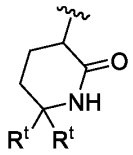
wherein ss is selected from 0, 1, 2, and 3, and mm is selected from 1, 2, and 3.

[00018] In some embodiments, disclosed herein are compounds represented by Formula II-I:

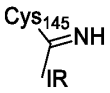


Formula II-I,

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is  or  ; R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl; R^B is selected from the group consisting of: a 9-10 membered bicyclic heteroaryl having one ring nitrogen, C_1-C_6alkyl, and C_2-C_3alkenyl; wherein R^B is optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_3alkoxy, NHR^m, and phenyl (optionally substituted by one or two halogens); and R^m is C_1-C_3alkyl or -C(O)-C_{1-3}alkyl, wherein each C_1-C_3alkyl is independently optionally substituted by one, two or three halogens.

[00019] In certain embodiments, disclosed herein are conjugates represented by Formula III:



Formula III,

wherein Cys_{145} is cysteine at position 145 or equivalent active site cysteine on a CL or 3CL protease; IR is a viral protease inhibitor; and wherein the compound that forms the conjugate comprises a -CN warhead.

DETAILED DESCRIPTION

[00020] The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions

should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

[00021] The term "treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like, including a reduction of viral shedding in asymptomatic individuals and prophylaxis of exposed individuals, independent of symptoms.

[00022] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C_{1-6}alkyl, C_{1-4}alkyl, and C_1-C_3alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

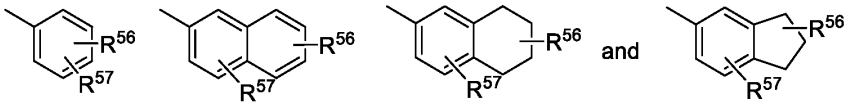
[00023] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Exemplary alkynyl groups include, but are not limited to, straight or branched groups of 2-6, or 3-6 carbon atoms, referred to herein as C_{2-6}alkynyl, and C_{3-6}alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, etc.

[00024] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein as C_1-C_5alkenyl, C_2-C_6alkenyl, and C_3-C_4alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

[00025] The term "alkoxy" as used herein refers to a straight or branched alkyl group attached to oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C_1-C_5alkoxy, C_1-C_6alkoxy, and C_2-C_6alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

[00026] The term "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, and trinaphthalene. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

[00027] Examples of representative substituted aryls include the following:



wherein one of R^{56} and R^{57} may be hydrogen and at least one of R^{56} and R^{57} is each independently selected from halogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, 4-10 membered heterocyclyl, alkanoyl, C_1-C_8 alkoxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, $NR^{58}COR^{59}$, $NR^{58}SOR^{59}$ $NR^{58}SO_2R^{59}$, COO-alkyl, COO-aryl, $CONR^{58}R^{59}$, $CONR^{58}OR^{59}$,

$NR^{58}R^{59}$, $SO_2NR^{58}R^{59}$, S-alkyl, SO-alkyl, SO_2-alkyl, S-aryl, SO-aryl, and SO_2-aryl; or R^{56} and R^{57} may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group consisting of N, O, and S; R^{60} and R^{61} are independently hydrogen, C_1-C_8 alkyl, C_1-C_4 haloalkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, 5-10 membered heteroaryl, or substituted 5-10 membered heteroaryl.

[00028] The term "carbonyl" as used herein refers to the radical -C(O)-.

[00029] The term "cyano" as used herein refers to the radical -CN.

[00030] The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to oxygen (cycloalkyl-O-). Exemplary cycloalkoxy groups include, but are not limited to, cycloalkoxy groups of 3-6 carbon atoms, referred to herein as C_{3-6}cycloalkoxy groups. Exemplary cycloalkoxy groups include, but are not limited to, cyclopropoxy, cyclobutoxy, cyclohexyloxy, etc.

[00031] The terms "cycloalkyl" or a "carbocyclic group" as used herein refers to a saturated or partially unsaturated hydrocarbon group of, for example, 3-6, or 4-6 carbons, referred to herein as C_3-C_{10}cycloalkyl, C_{3-6}cycloalkyl or C_{4-6}cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl or cyclopropyl.

[00032] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

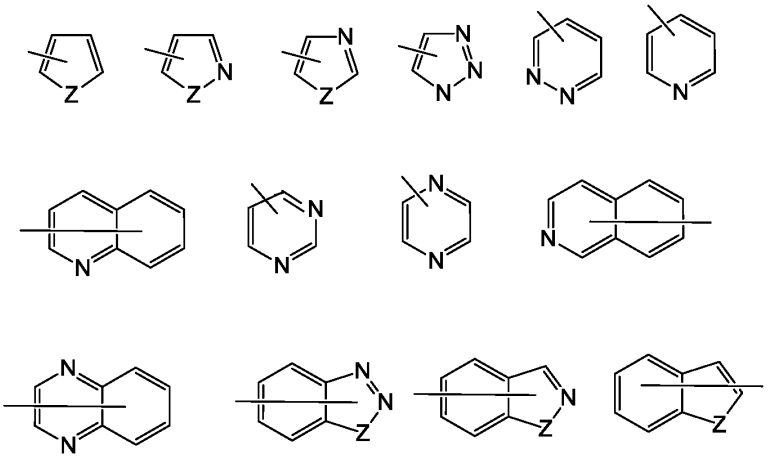
[00033] The term "haloalkyl" as used herein refers to an alkyl radical in which the alkyl group is substituted with one or more halogens. Typical haloalkyl groups include, but are not limited to, trifluoromethyl (i.e. CF_3), difluoromethyl, fluoromethyl, chloromethyl, dichloromethyl, dibromoethyl, tribromomethyl, tetrafluoroethyl, and the like. Exemplary haloalkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms substituted with a halogen (i.e. Cl, F, Br and I), referred to herein as C_{1-6}haloalkyl, C_{1-4} haloalkyl, and C_{1-3}haloalkyl, respectively.

[00034] The term "hetero" when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been

replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, *e.g.*, heteroalkyl, cycloalkyl, *e.g.*, heterocyclyl, aryl, *e.g,*. heteroaryl, cycloalkenyl, *e.g,*. cycloheteroalkenyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[00035] The terms "heteroaryl" or "heteroaromatic group" as used herein refers to an aromatic 5-10 membered ring system containing one or more heteroatoms, for example one to three heteroatoms, such as nitrogen, oxygen, and sulfur. The term may also be used to refer to a 5-7 membered monocyclic heteroaryl or an 8-10 membered bicyclic heteroaryl. Where possible, said heteroaryl ring may be linked to the adjacent radical though carbon or nitrogen. Examples of heteroaryl rings include but are not limited to furan, thiophene, pyrrole, pyrrolopyridine, indole, thiazole, oxazole, isothiazole, isoxazole, imidazole, benzoimidazole, imidazopyridine, pyrazole, triazole, pyridine or pyrimidine, etc.

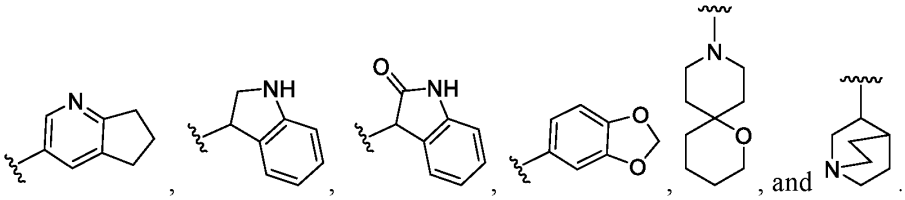
[00036] Examples of representative heteroaryls include the following:



wherein each Z is selected from carbonyl, N, NR^{65}, O, and S; and R^{65} is each independently hydrogen, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, and 5-10 membered heteroaryl.

[00037] The terms "heterocyclyl," "heterocycle," or "heterocyclic group" are art-recognized and refer to saturated or partially unsaturated 4-10 membered ring structures, whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and

sulfur. Where possible, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. The term may also be used to refer to 4-10 membered saturated or partially unsaturated ring structures that are bridged, fused or spirocyclic ring structures, whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran, dihydrofuran, dihydropyran, tetrahydropyran, etc. In some embodiments, the heterocycle is a spiro heterocycle (e.g., 2,8-diazaspiro[4.5]decane). In some embodiments, the heterocycle is a bridged heterocycle (e.g., octahydro-1H-4,7-methanoisoindole). "Spiro heterocyclyl," or "spiro heterocycle" refers to a polycyclic heterocyclyl with rings connected through one common atom (called a spiro atom), wherein the rings have one or more heteroatoms selected from the group consisting of N, O, and $S(O)_m$ (wherein m is an integer of 0 to 2) as ring atoms. Representative examples of heterocyclyl include, for example:



, and .

[00038] The term "heterocyclyloxy" as used herein refers to a heterocyclyl group attached to oxygen (heterocyclyl-O-).

[00039] The term "heteroaryloxy" as used herein refers to a heteroaryl group attached to oxygen (heteroaryl-O-).

[00040] The terms "hydroxy" and "hydroxyl" as used herein refers to the radical -OH.

[00041] The term "oxo" as used herein refers to the radical =O.

[00042] "Pharmaceutically or pharmacologically acceptable" include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

[00043] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well-known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[00044] The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[00045] “Individual,” “patient,” or “subject” are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like). “Modulation” includes antagonism (*e.g.*, inhibition), agonism, partial antagonism and/or partial agonism.

[00046] In the present specification, the term “therapeutically effective amount” means the amount of the subject compound that will elicit the biological or medical response of a tissue, system or animal, (e.g. mammal or human) that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds of the disclosure are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect.

[00047] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic

compounds are those that form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[00048] The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term "stereoisomers" when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols "(+)," "(-)," "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present disclosure encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[00049] The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol ⎓ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*" are used in accordance with IUPAC standards. Unless otherwise specified,

structures depicting double bonds encompass both the *"E"* and *"Z"* isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond.

[00050] Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. The arrangement of substituents around a carbocyclic or heterocyclic ring are designated as being in the *"Z"* or *"E"* configuration wherein the terms *"Z"* and *"E"* are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both *"Z"* and *"E"* isomers. Substituents around a carbocyclic or heterocyclic rings may also be referred to as "cis" or "trans", where the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[00051] Individual enantiomers and diastereomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well-known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well-known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations, and may

involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[00052] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

[00053] The disclosure also embraces isotopically labeled compounds of the disclosure which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. For example, a compound of the disclosure may have one or more H atom replaced with deuterium.

[00054] Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the disclosure can generally be prepared by following procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[00055] The term "prodrug" refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such

as in the intestinal lumen or upon transit of the intestine, blood or liver). Prodrugs are well-known in the art (for example, see Rautio, Kumpulainen, *et al.*, Nature Reviews Drug Discovery 2008, 7, 255). For example, if a compound of the disclosure or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_{1-8})alkyl, (C_{2-12})alkylcarbonyloxymethyl, 1-(alkylcarbonyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkylcarbonyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_{1-2})alkylamino(C_{2-3})alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_{1-2})alkyl, N,N-di(C_{1-2})alkylcarbamoyl-(C_{1-2})alkyl and piperidino-, pyrrolidino- or morpholino(C_{2-3})alkyl.

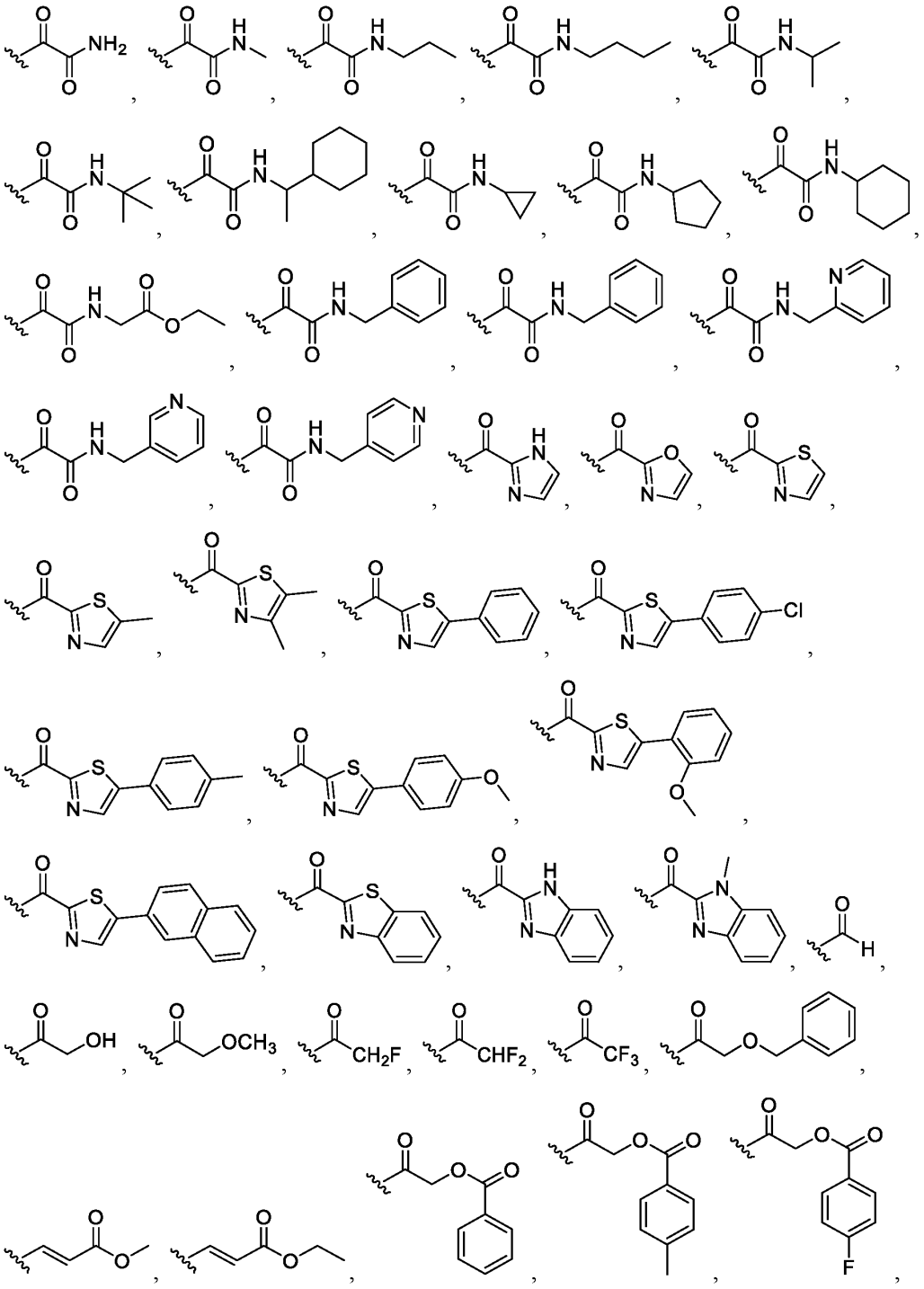
[00056] Similarly, if a compound of the disclosure contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkylcarbonyloxymethyl, 1-((C_{1-6})alkylcarbonyloxy)ethyl, 1-methyl-1-((C_{1-6})alkylcarbonyloxy)ethyl (C_{1-6})alkoxycarbonyloxymethyl, N-(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkylcarbonyl, α-amino(C_{1-4})alkylcarbonyl, arylalkylcarbonyl and α-aminoalkylcarbonyl, or α-aminoalkylcarbonyl-α-aminoalkylcarbonyl, where each α-aminoalkylcarbonyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_{1-6})alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

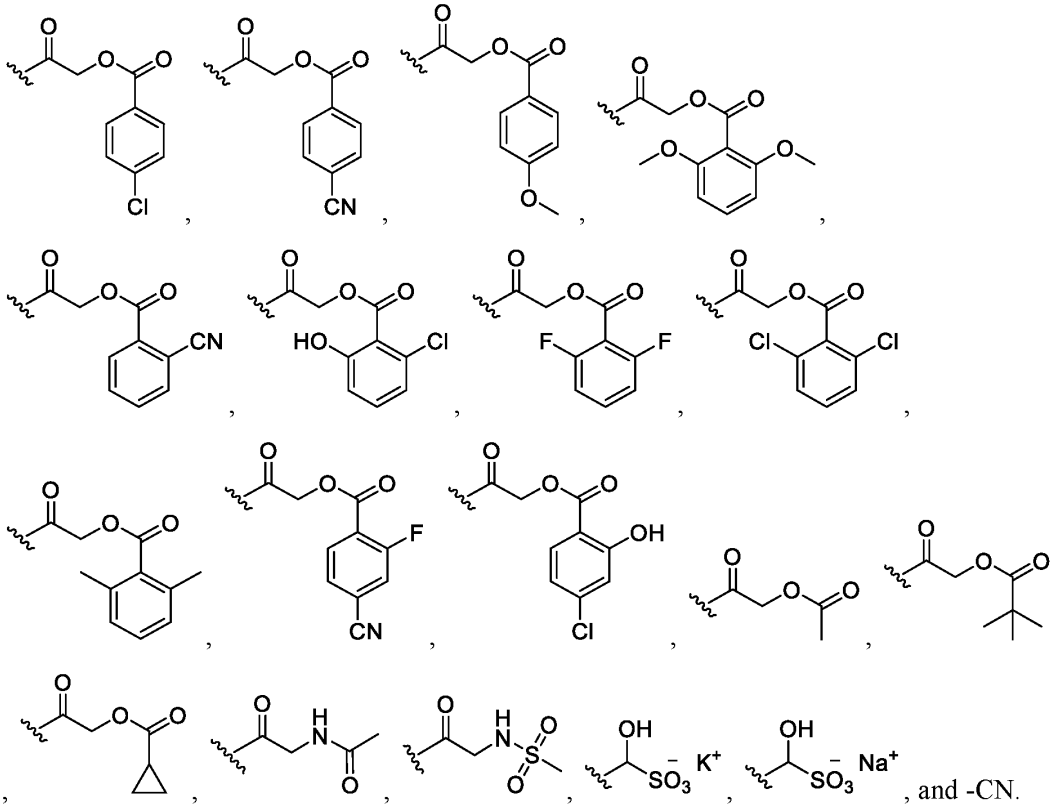
[00057] If a compound of the disclosure incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-alkylcarbonyloxyalkyl derivative, an (oxodioxolenyl)methyl derivative, an N-Mannich base, imine or enamine. In addition, a secondary amine can be metabolically cleaved to generate a bioactive primary amine, or a tertiary amine can metabolically cleaved to

generate a bioactive primary or secondary amine. For examples, see Simplício, *et al.*, *Molecules* 2008, *13,* 519 and references therein.

[00058] The term "warhead" or "warhead group" as used herein refers to a functional group present on a compound wherein that functional group is capable of reversibly or irreversibly participating in a reaction with a protein, e.g., 3C or 3CL protease (e.g., with a cysteine on the protease such as Cys 145). Warheads may, for example, form covalent bonds with the protein, or may create stable transition states, or be a reversible or an irreversible alkylating agent. For example, the warhead moiety can be a functional group on an inhibitor that can participate in a bond-forming reaction, wherein a new covalent bond is formed between a portion of the warhead and a donor, for example an amino acid residue of a protein. In embodiments, the warhead is an electrophile and the "donor" is a nucleophile such as the side chain of a cysteine residue. As provided herein, a warhead may include a nitrile or halo group. As also provided herein, a warhead may include an aldehyde, ketoamides, hydroxybisulfite salts, heterocyclic moieties, aziridine, oxirane, epoxy ketones, halomethyl ketones, hydroxymethyl ketones, electrophilic ketones (e.g. trifluoromethyl ketones), acyloxymethyl ketones, benzothiazolyl ketones and a Michael acceptor. For example, nitriles may be reversible covalent warheads for cysteine protease inhibition, for example, where the mechanism of action may involve formation of a reversible covalent bond between the nitrile and the active cysteine to form a thioimidate adduct. Reaction of cysteine of glutathione or other proteins is generally reversible, while the reaction with cysteine or aminoethylthiols generally irreversibly forms a thiazolidine adduct. It can be appreciated that contemplated compounds herein may be a reversible or an irreversible inhibitor.

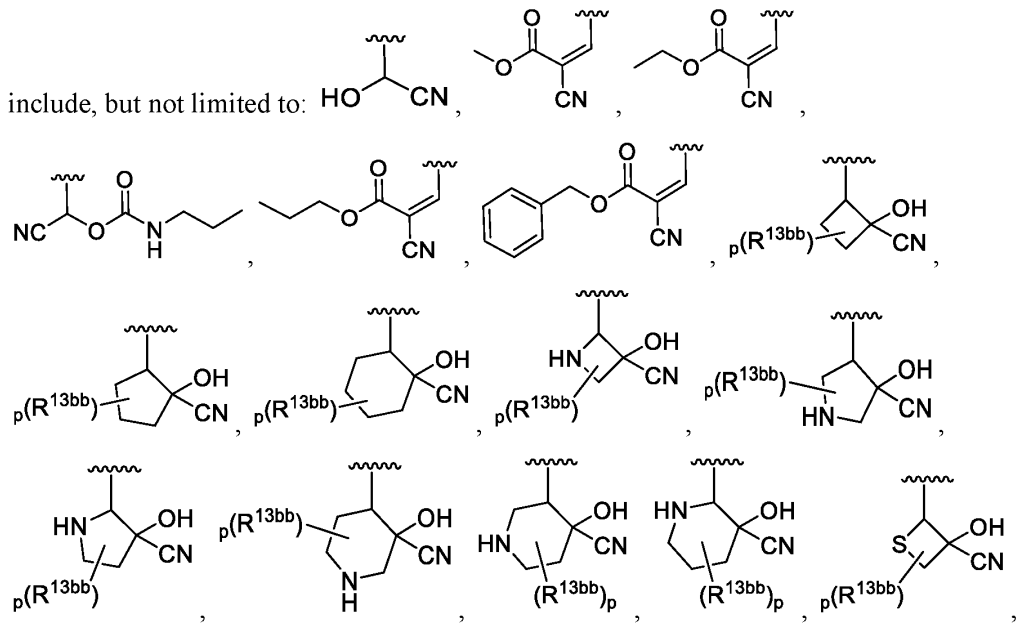
[00059] Examples of exemplary warheads include, but not limited to, a moiety with a cyano, halomethyl, aldehyde, ketoamide, hydroxybisulfite salt, heterocycle, epoxy ketone, halomethyl ketone, hydroxymethyl ketone, electrophilic ketone, acyloxymethyl ketone, benzothiazolyl ketone or a Michael acceptor, for example:

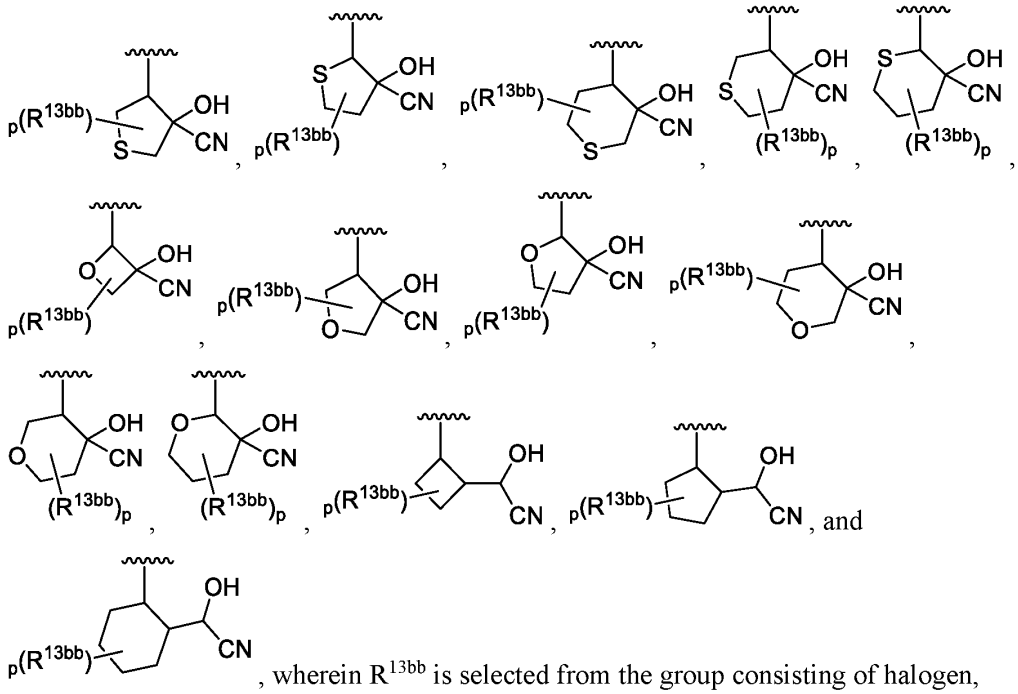




, and -CN.

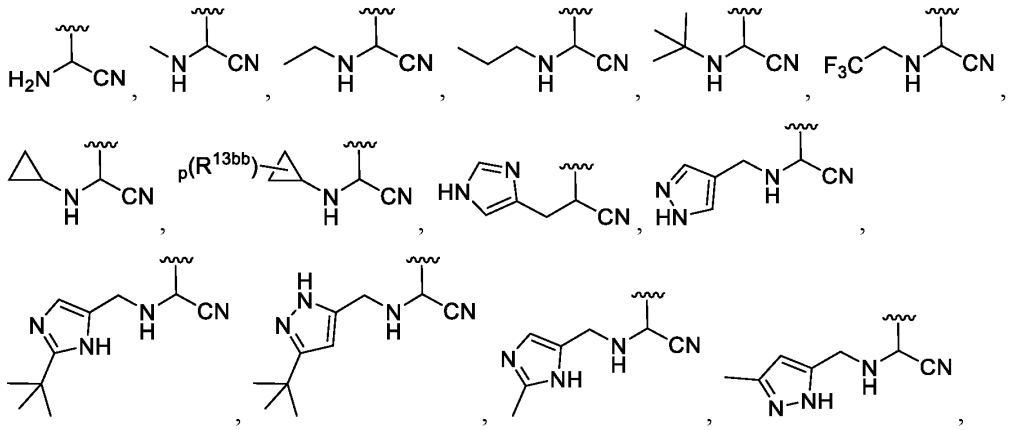
[00160] In some embodiments, the warhead is a moiety with a cyanohydrin or cyanoacrylate moiety. Examples of exemplary cyanohydrin and cyanoacrylate warheads include, but not limited to:

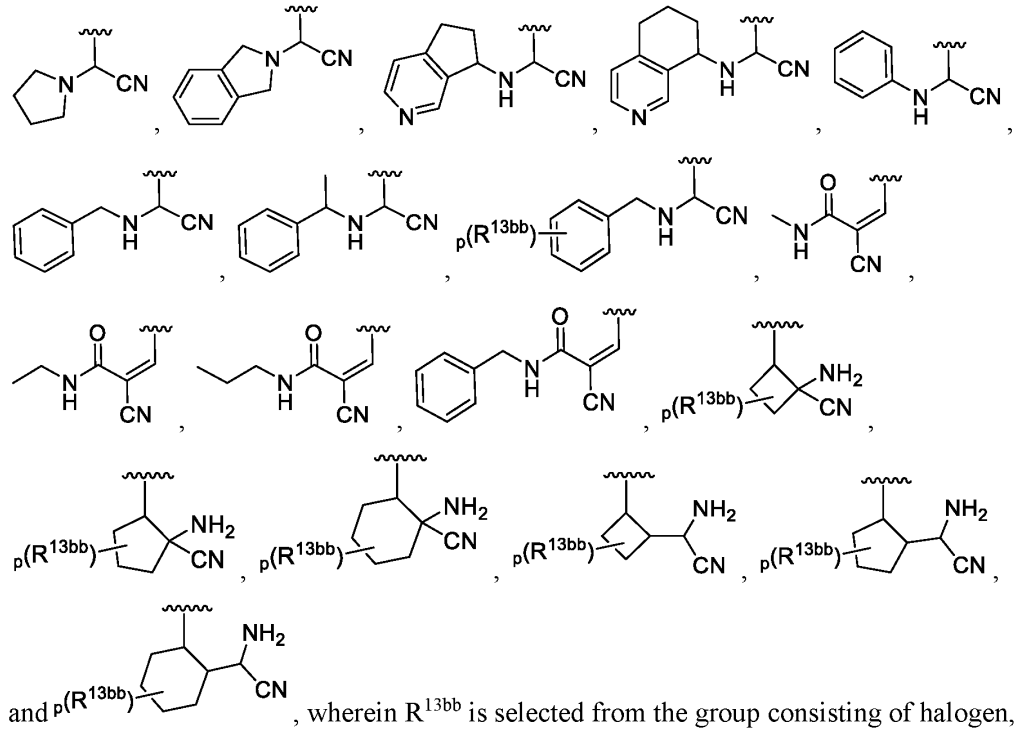




, wherein R^{13bb} is selected from the group consisting of halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, -$N(R^eR^f)$, and -$C(O)$-$N(R^eR^f)$; R^e and R^f are each selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^e and R^f may form, together with the nitrogen to which they are attached, a 4-6 membered heterocycle; and p is 0, 1, 2, 3, or 4, as valency permits.

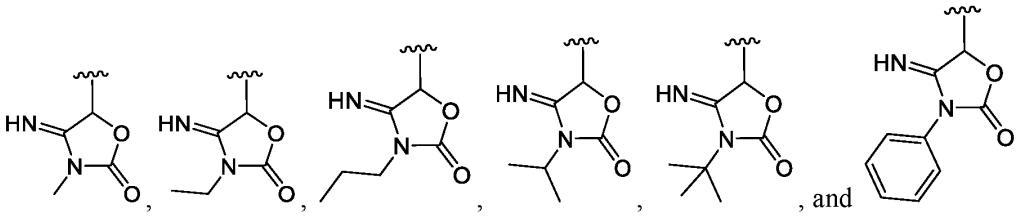
[00061] In some embodiments, the warhead is a moiety with a cyano amine or cyano amide moiety. Examples of exemplary cyanoamine warheads include, but not limited to:





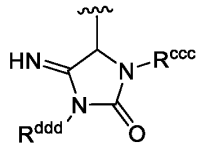
and , wherein R^{13bb} is selected from the group consisting of halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_3-C_{10}cycloalkyl, -N(R^eR^f), and -C(O)-N(R^eR^f); R^e and R^f are each selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^e and R^f may form, together with the nitrogen to which they are attached, a 4-6 membered heterocycle; and p is 0, 1, 2, 3, or 4, as valency permits.

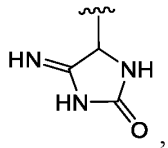
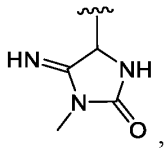
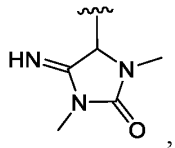
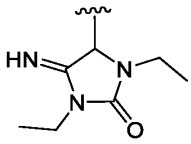
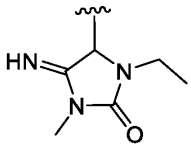
[00062] In some embodiments, the warhead is a moiety with an imino-oxazolidinone moiety. Examples of exemplary imino-oxazolidinone warheads include, but not limited to:

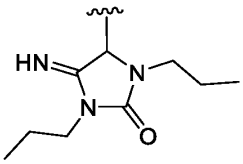
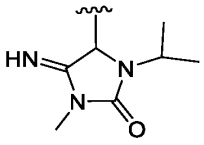
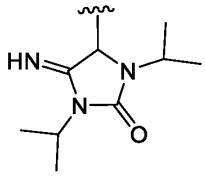
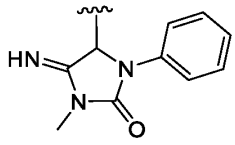


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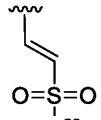
[00063] In some embodiments, the warhead is a moiety with an iminoimidazolidinone. Examples of exemplary iminoimidazolidinone warheads include, but not limited to:

[00064]  , wherein each R^{ccc} and R^{ccc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), and C_6-C_{14}aryl. In some embodiments, the warhead is selected from the group consisting of

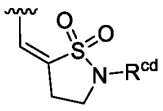
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 ,  ,  , and  .

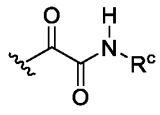
[00065] Other examples of exemplary warheads include, but not limited to:

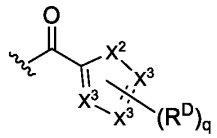
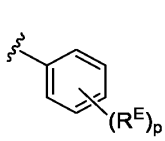
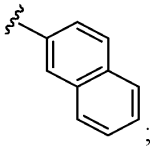
 , wherein R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle.

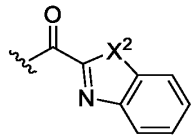
[00066] Some other examples of exemplary warheads include, but not limited to:

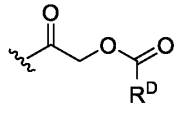
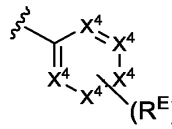
 , wherein R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl.

[00067] Other examples of exemplary warheads include, but not limited to:


, wherein R^c is selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), C_1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl;


, wherein X^2 is selected from the group consisting of NH, O and S; X^3 is independently selected, for each occurrence, from N and CH; R^D is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl,  and  ; R^E is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, C_1-C_8alkyl and C_1-C_8alkoxy; p is selected from 0, 1 and 2; and q is selected from 0, 1 and 2;


, wherein X^2 is selected from the group consisting of NH, NR^P, O and S, wherein R^P is C_1-C_8alkyl;


, wherein R^D is selected from the group consisting of C_3-C_6cycloalkyl, C_1-C_8alkyl, and  ; X^4 is independently selected, for each occurrence, from CH and N; R^E is independently selected, for each occurrence, from the group consisting of halogen, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, -CN, $-CF_3$, $-OCF_3$ and $-SCF_3$; and p is selected from 0, 1 and 2; –$C(O)R^D$, wherein R^D is selected from the group consisting of hydrogen, $-CH_2OH$, $-CH_2OR'$ and $-CH_xF_y$, wherein x is 0, 1 or 2; y is 1, 2 or 3; and the sum of x and y is 3, wherein

$R^{'}$ is selected from the group consisting of C_1-C_8alkyl, -(C_1-C_8alkyl)-(5-10 membered aryl), C_1-C_8heteroalkyl, C_3-C_6cycloalkyl and 5-10 membered aryl; and –(CH=CH)C(O)OR^D, wherein R^D is C_1-C_8alkyl.

[00068] It will be appreciated to one of skill in the art that the compounds disclosed herein that include the warheads above also contemplate the precursors to those compounds, for example, where a cyano moiety involved in a warheads may be replaced with e.g., a halo moiety.

[00069] It will be appreciated to one of skill in the art that the compounds disclosed herein can also irreversibly bind, or may otherwise inhibit e.g., a virus protein via any other mechanism of action.

[00070] The term "inhibitor" as used herein refers to a compound that binds to and/or inhibits a target protease with measurable affinity.

[00071] The term “reversible” or "reversible inhibitor" as used herein refers to a protease inhibitor that associates with a protease in such a way as to inhibit the activity of the protease while the protease and inhibitor are bound, but does not associate with a protease in such a way as to inhibit the activity of the protease when the protease and inhibitor are no longer bound. Reversible inhibitors can effect inhibition by competing with substrate for binding to the active site of the protease (competitive reversible inhibitor), or by associating with the protease bound to its substrate in a way to make the complex inactive (uncompetitive reversible inhibitor), or by associating with the protease and/or protease-substrate complex in a way that inhibits the activity of either and/or both.

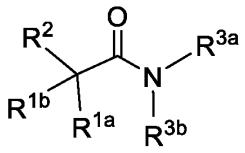
[00072] As used herein, the term “irreversible” or “irreversible inhibitor” refers to an inhibitor (i.e. a compound) that is able to be covalently bonded to a target protease in a substantially non-reversible manner. An irreversible inhibitor will remain substantially bound to the target protease once covalent bond formation has occurred. Irreversible inhibitors usually display time dependency, whereby the degree of inhibition increases with the time with which the inhibitor is in contact with the enzyme. In certain embodiments, an irreversible inhibitor will remain substantially bound to target

protease once covalent bond formation has occurred, and will remain bound for a time period that is longer than the life of the protein.

I. Reversible or Irreversible Viral Protease Inhibitor Compounds

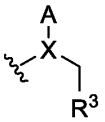
[00073] The disclosure is directed to, in part, compounds that inhibit a viral protease. Examples of viral proteases include, but not limited to, Cathepsin K, coronavirus main protease (Mpro), Caspase 3, Calpain 1, and Cathepsin S. Accordingly, in various embodiments, a compound of the present disclosure (e.g. a compound of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A or IV-B) is a viral protease inhibitor, wherein the viral protease is selected from the group consisting of Cathepsin K, coronavirus main protease (Mpro), Caspase 3, Calpain 1, and Cathepsin S. In certain embodiments, the viral protease is a coronavirus main protease (Mpro). In some embodiments, the viral protease is Cathepsin K. In some embodiments, the viral protease is Caspase 3. In some embodiments, the viral protease is Calpain 1. In some embodiments, the viral protease is Cathepsin S.

[00074] Also provided herein are compounds represented by



Formula II,

or a pharmaceutically acceptable salt, stereoisomer, ester, or prodrug thereof, wherein:

R^{3a} is selected from 

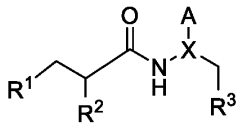
and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A; R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected

from C_6-C_{14}aryl and a warhead A; R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl; R^{1b} is selected from hydrogen and C_1-C_8alkyl; or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen, NR^G, or a C_3-C_{10}cycloalkyl; R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A; R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, $–CH_2CF_3$, $–CF_3$, $–O-CF_3$, $–O-CHF_2$, $–S-CH_3$, $–S(O)_2-CH_3$, $–NH_2$, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, $–NHC(O)R^B$, $–NHC(O)OR^B$, $–NHC(O)O-(C_1$-C_8alkyl)-R^B, $–N(R^y)_2$, $–N(R^y)(C_1$-C_8alkyl)C(O)O-phenyl, $–N(R^y)(C_1$-C_8alkyl)$C(O)N(R^y)_2$, $–C(O)-OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl and oxo; R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, –O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x; or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered monocyclic or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A; R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A; R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle; R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, -O-C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle; wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo, halogen and C_1-C_8alkyl; R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-C_{3-6}cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{ii}; R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m; R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy; R^{ii} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_{1-6}haloalkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2; R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -S(O)$_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo; R^{xx} is –(OCH_2CH_2)$_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6; R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH; A is a warhead; and X is selected from the group consisting of C(R^{xy}) and N, wherein R^{xy} is selected from the group consisting of H, D, -OH, -NH_2, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy.

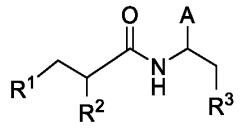
[00075] In some embodiments, R^{3b} is hydrogen.

[00076] In certain embodiments, disclosed herein are compounds represented by Formula II-A:



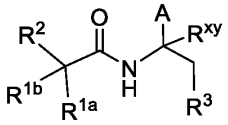
Formula II-A.

[00077] In certain embodiments, disclosed herein are compounds represented by Formula II-B:



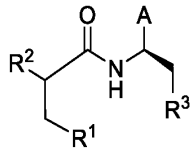
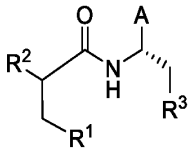
Formula II-B.

[00078] In various embodiments, disclosed herein are compounds represented by Formula II-C:

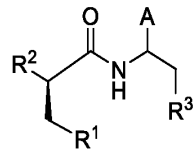
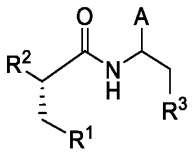


Formula II-C.

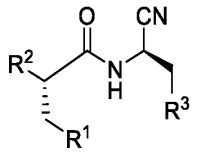
[00079] In some embodiments, disclosed herein are compounds represented by Formula II-D-A or Formula II-D-B:

 (Formula II-D-A) or  (Formula II-D-B).

[00080] In some embodiments, disclosed herein are compounds represented by Formula II-E-A or Formula II-E-B:

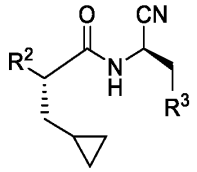
 (Formula II-E-A) or  (Formula II-E-B).

[00081] In some embodiments, provided herein are compounds represented by Formula II-F:



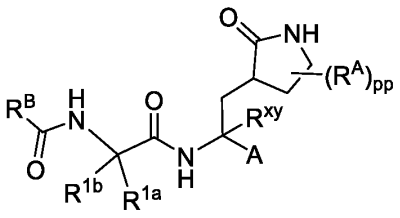
Formula II-F.

[00082] In some embodiments, provided herein are compounds represented by Formula II-G:

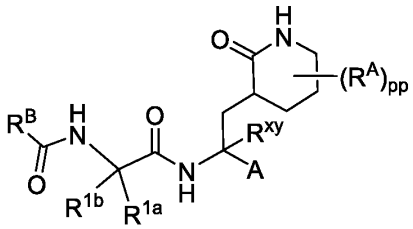


Formula II-G.

[00083] In some embodiments, disclosed herein are compounds represented by Formula II-H-A or Formula II-H-B:



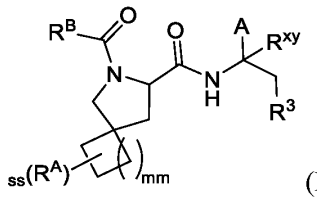
(Formula II-H-A), or



(Formula II-H-B),

wherein pp is selected from 0, 1, 2, and 3.

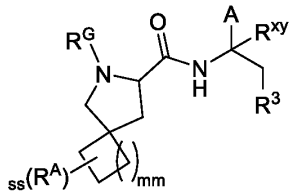
[00084] In some embodiments, disclosed herein are compounds represented by Formula II-E:



(Formula II-E),

wherein ss is selected from 0, 1, 2, and 3, and mm is selected from 1, 2, and 3.

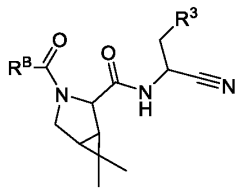
[00085] In other embodiments, disclosed herein are compounds represented by Formula II-E-II:



(Formula II-E-II),

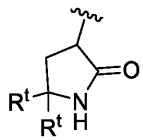
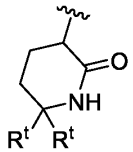
wherein ss is selected from 0, 1, 2, and 3, and mm is selected from 1, 2, and 3.

[00086] In some embodiments, disclosed herein are compounds represented by Formula II-I:

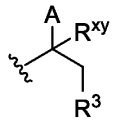


Formula II-I,

or a pharmaceutically acceptable salt thereof, wherein:

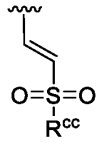
R^3 is  or  ; R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl; R^B is selected from the group consisting of: a 9-10 membered bicyclic heteroaryl having one ring nitrogen, C_1-C_6alkyl, and C_2-C_3alkenyl; wherein R^B is optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_3alkoxy, NHR^m, and phenyl (optionally substituted by one or two

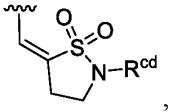
halogens); and R^m is C_{1-3}alkyl or -C(O)-C_{1-3}alkyl, wherein C_{1-3}alkyl is independently optionally substituted by one, two or three halogens.

[00087] In certain embodiments, R^{3a} is 

, wherein R^{xy} is selected from the group consisting of H, D, OH, NH_2, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy. In embodiments, R^{xy} is selected from the group consisting of H, D, CH_3, CH_2CH_3, F, and CF_3. In some embodiments, R^{xy} is F. In some embodiments, R^{xy} is CF_3. In some embodiments, CH_3. In some embodiments, R^{xy} is H.

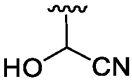
[00088] In various embodiments, X is selected from the group consisting of CH, CD, $C(CH_3)$, $C(CH_2CH_3)$, N, CF, CCl, CBr, $C(CHF_2)$, $C(CH_2F)$, and $C(CF_3)$. In some embodiments, X is CH. In some embodiments, X is CD. In some embodiments, X is $C(CH_3)$. In some embodiments, X is $C(CF_3)$. In some embodiments, X is CF. In some embodiments, X is N.

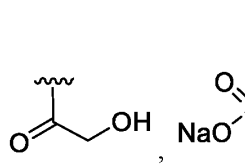
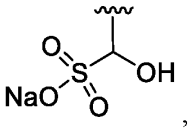
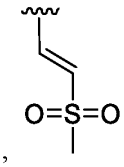
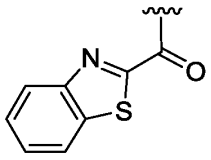
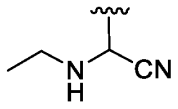
[00089] In some embodiments, A is selected from the group consisting of cyano, –$C(O)R^D$, –$C(O)CH_2N(R^bR^c)$, –$C(O)CH_2OC(O)R^D$, –$C(O)C(O)R^D$, –(CH=CH)$C(O)OR^D$, –(CH=CCN)$C(O)OR^D$, –(CH=CCN)$C(O)(NH)R^D$, –CH(CN)(OH), -CH(CN)(NR^bR^c), 

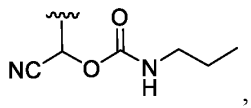
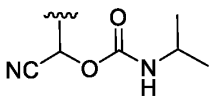
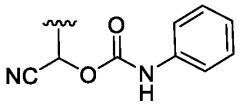
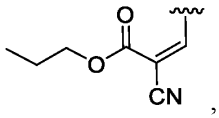
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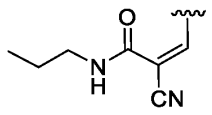
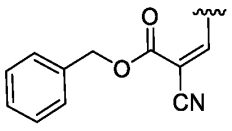
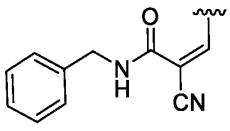
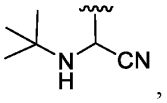
, wherein R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} –$N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each independently selected from the group consisting of halogen, hydroxyl, and R^E; R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each independently selected from the group consisting of halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy; R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-

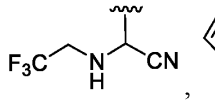
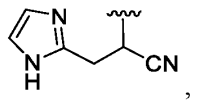
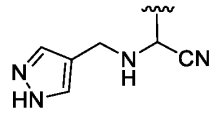
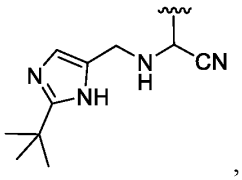
C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each independently selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle; R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

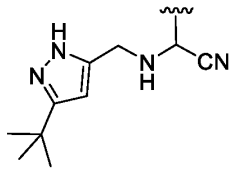
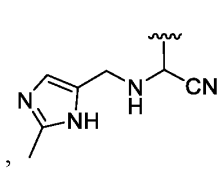
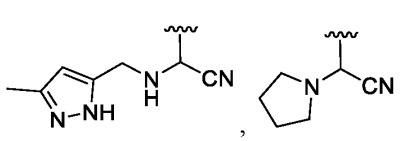
[00090] In embodiments, A is selected from the group consisting of -CN,  ,

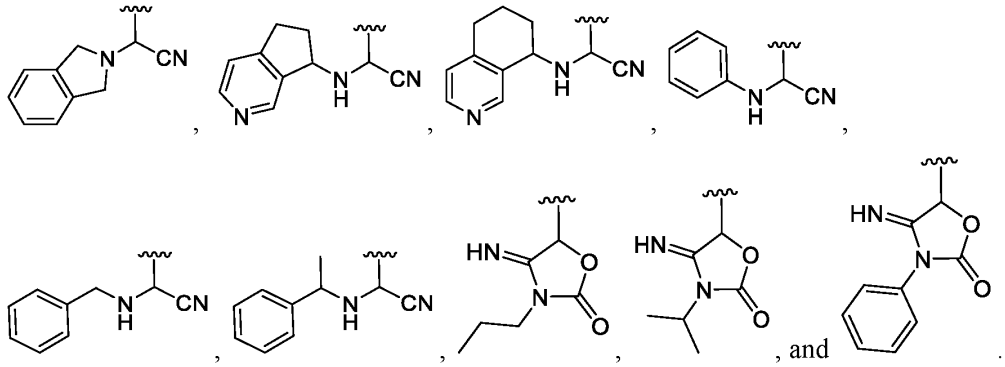
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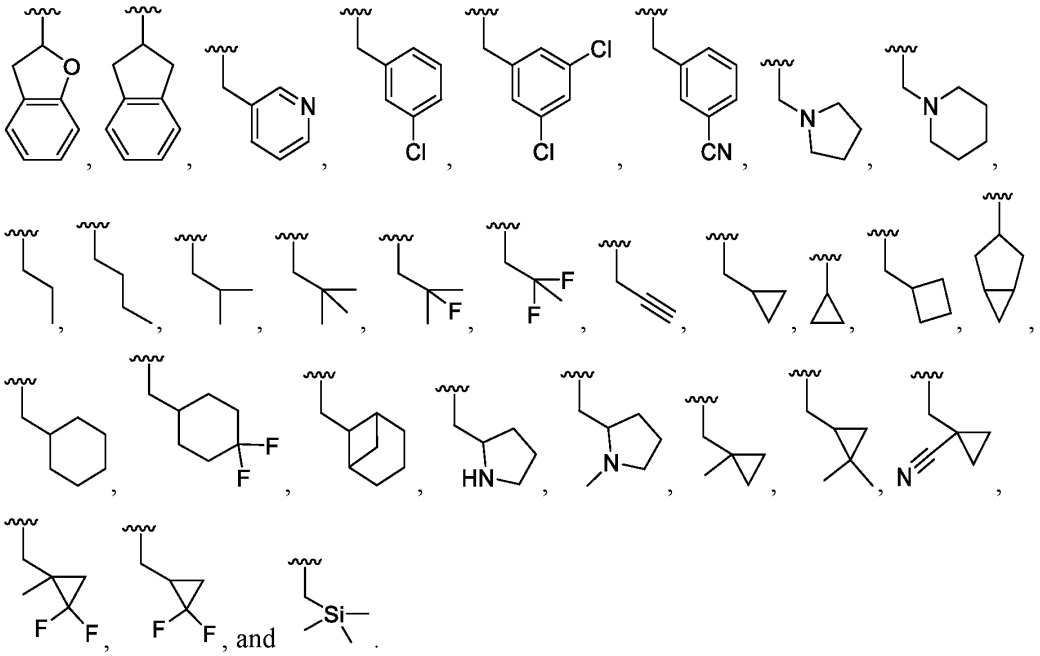
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[00091] In embodiments, R^{1a} is selected from the group consisting of



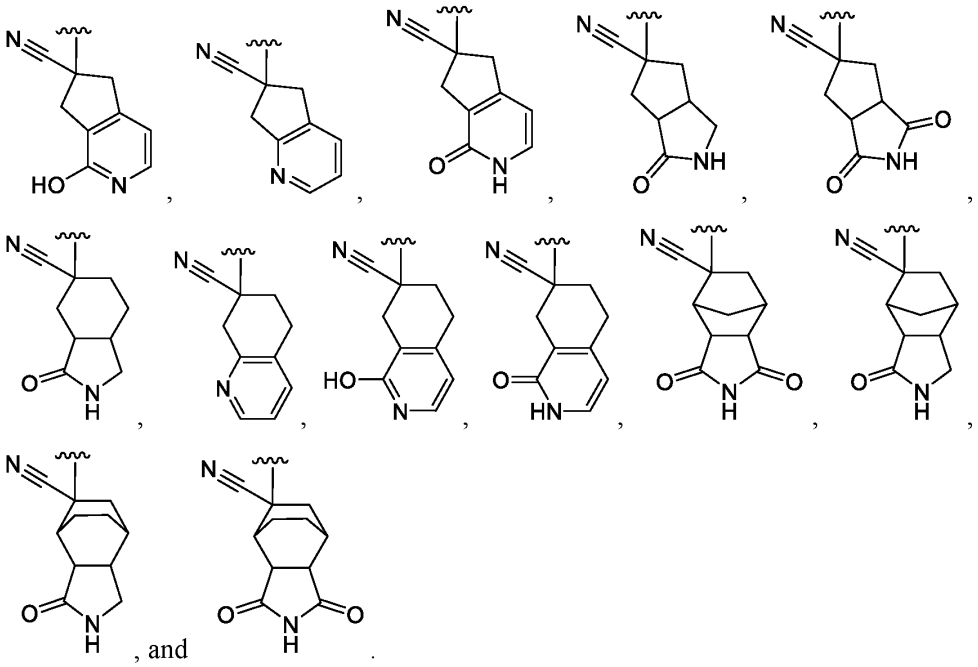
[00092] In embodiments, R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

[00093] In embodiments, R^{1b} is hydrogen.

[00094] In certain embodiments, R^{1a} and R^{1b} are joined to together to form  .

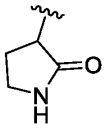
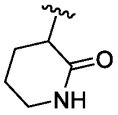
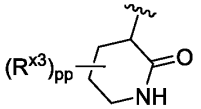
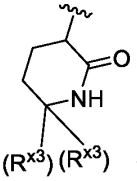
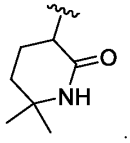
[00095] In certain embodiments, R^{3a} is a 4-10 membered heterocycle.

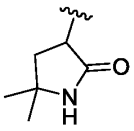
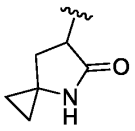
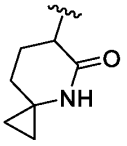
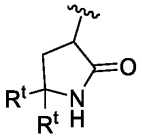
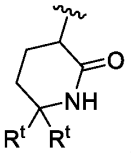
[00096] In some embodiments, R^{3a} is selected from the group consisting of

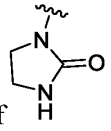
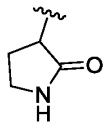
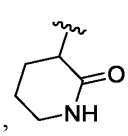
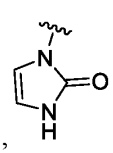
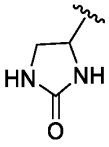
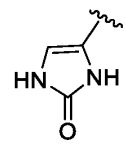
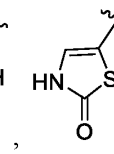
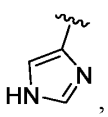
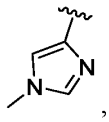
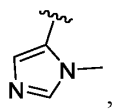
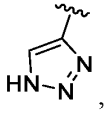
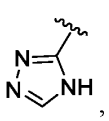
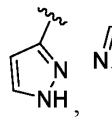
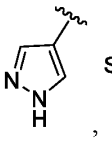
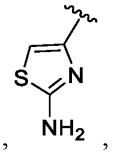
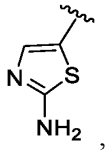
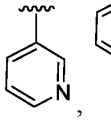
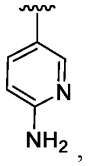
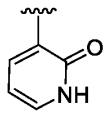
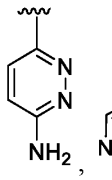
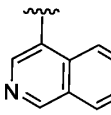
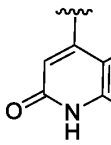
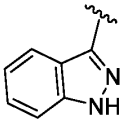
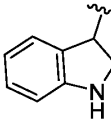
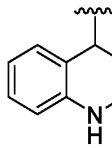
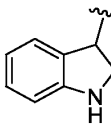
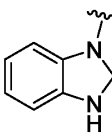
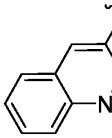
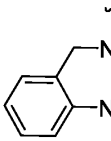
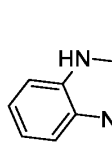
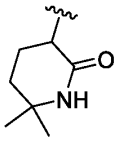
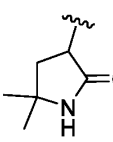
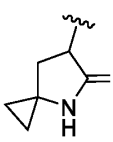
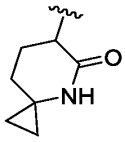
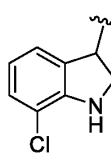


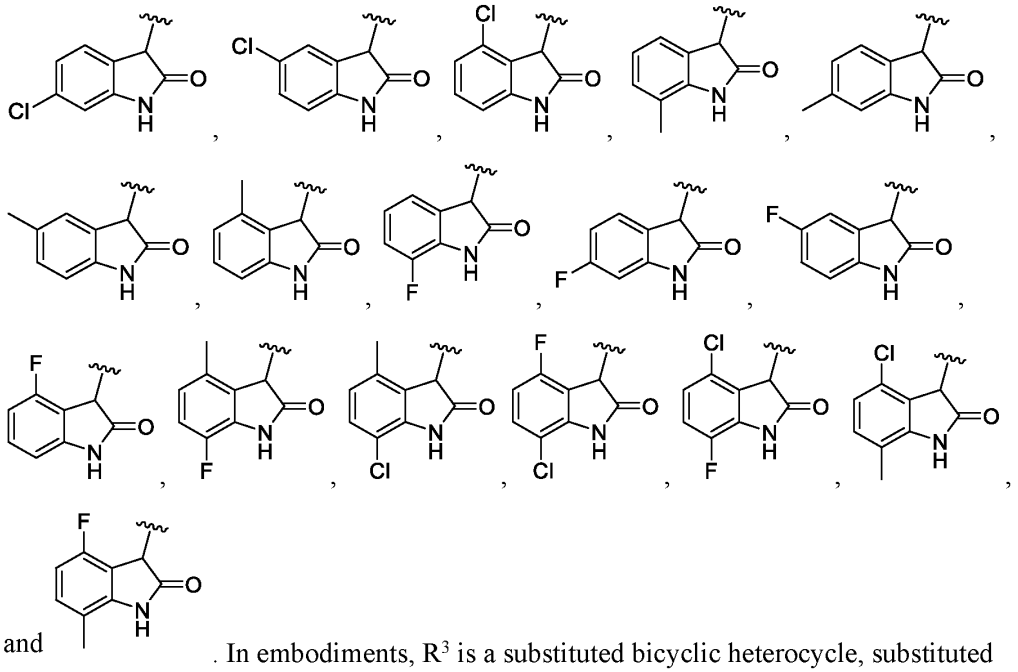
, and .

[00097] In some embodiments, R^3 is a 4-10 membered heterocycle.

[00098] In some embodiments, R^3 is selected from  and  . In some embodiments, R^3 is  , (for example, ), wherein R^{x3} are independently for each occurrence selected from the group consisting of hydrogen, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, C_3-C_6cycloalkyl, and C_1-C_8alkoxy; and pp is selected from 0, 1, 2, and 3. In some embodiments, R^3 is  . In some

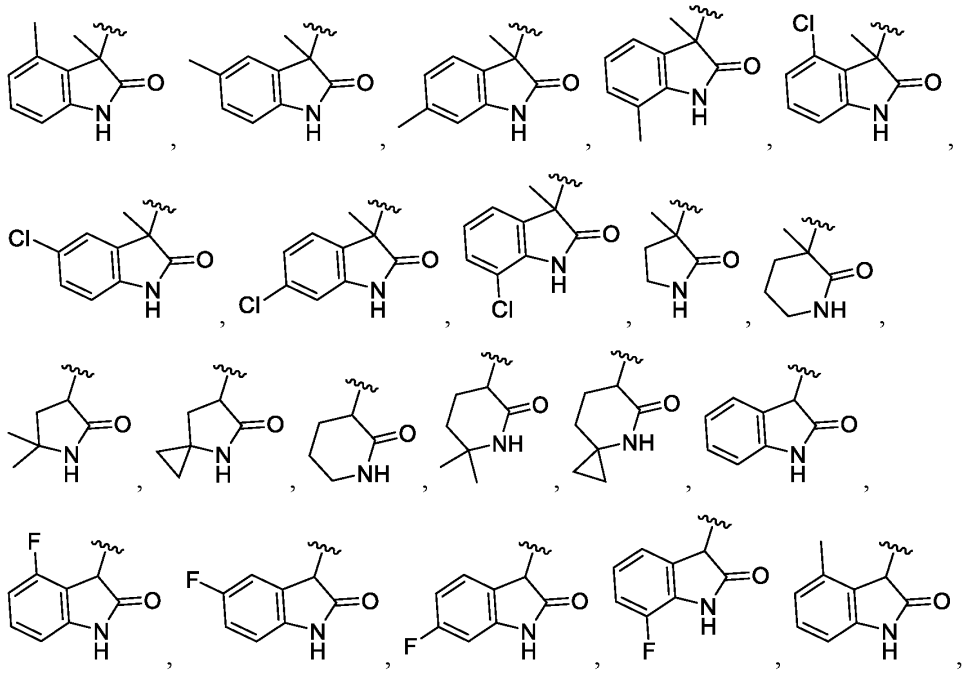
embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  or  , and R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl.

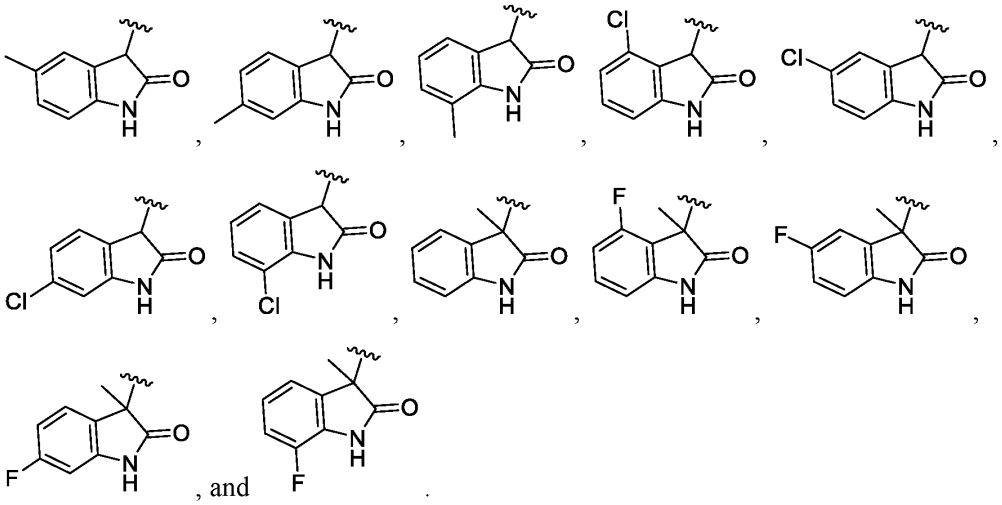
[00099] In some embodiments, R^3 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .



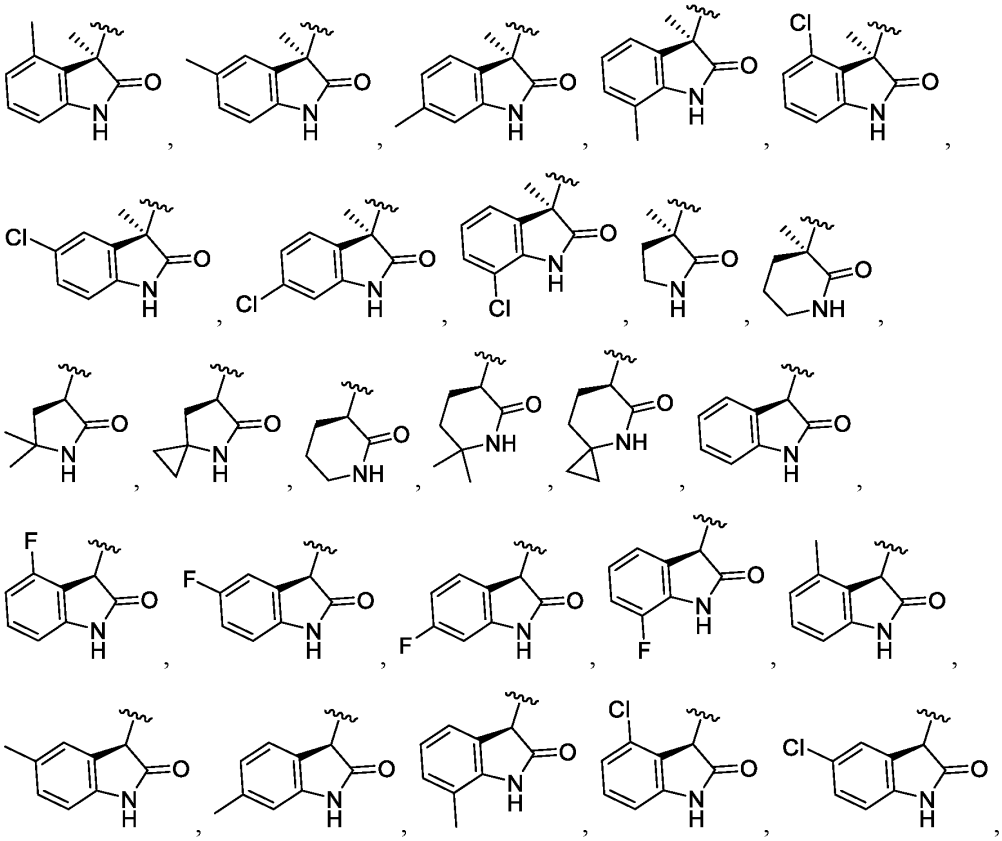
and . In embodiments, R^3 is a substituted bicyclic heterocycle, substituted monocyclic heterocycle, substituted bicyclic heteroaryl or substituted monocyclic heteroaryl.

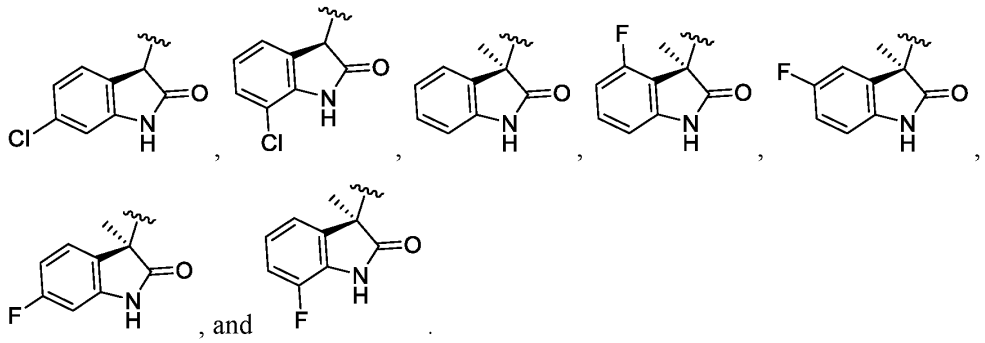
[000106] In some embodiments, R^3 is selected from the group consisting of




, and .

[000103] In some embodiments, R^3 is selected from the group consisting of

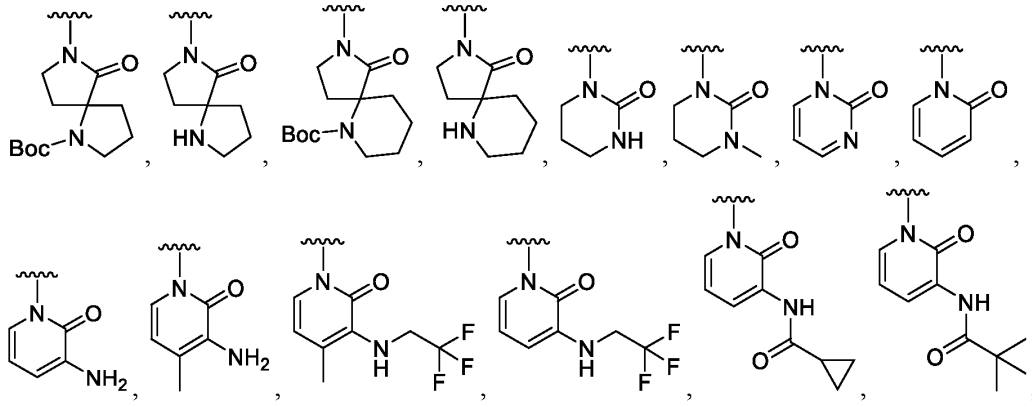


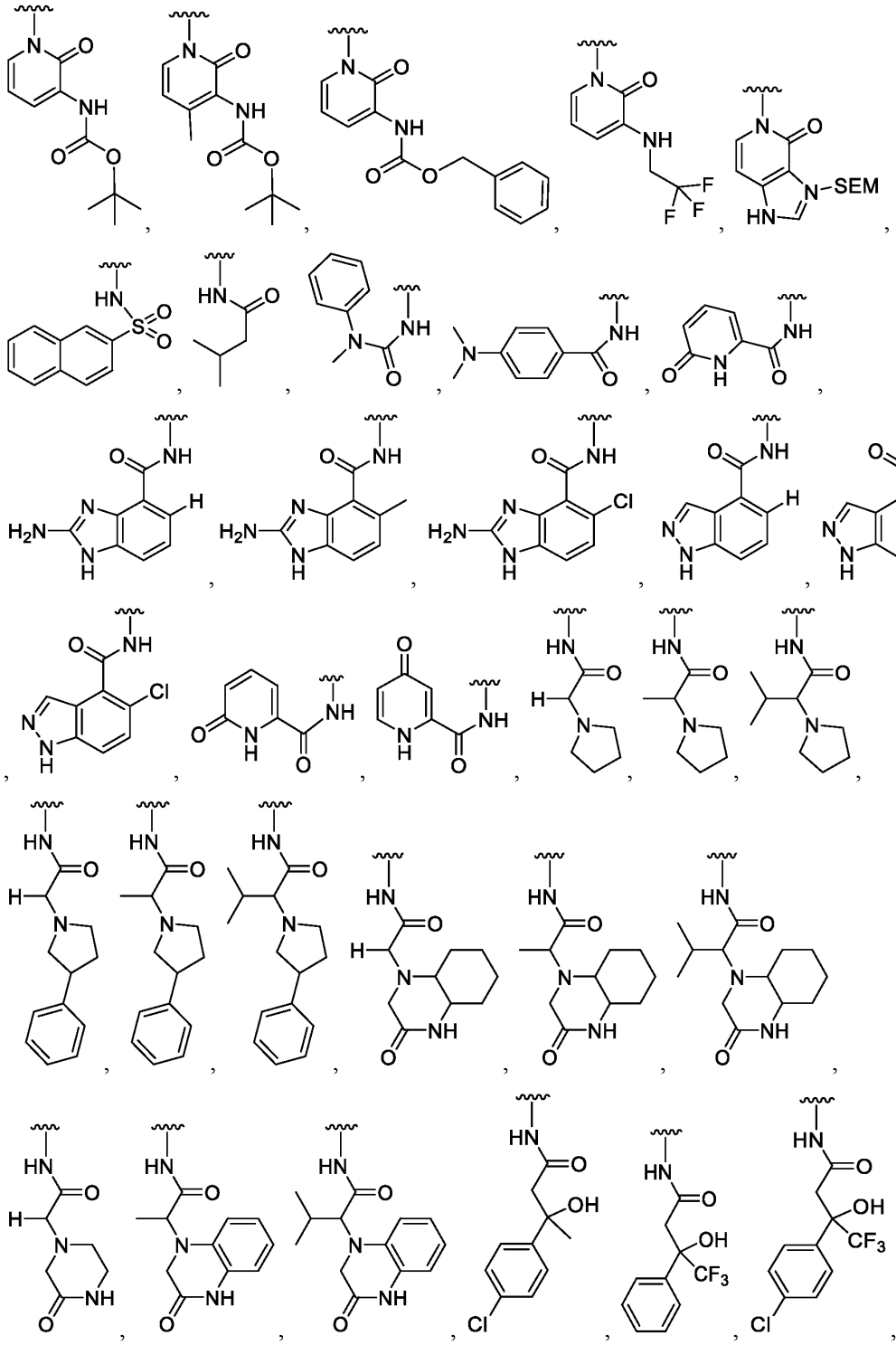


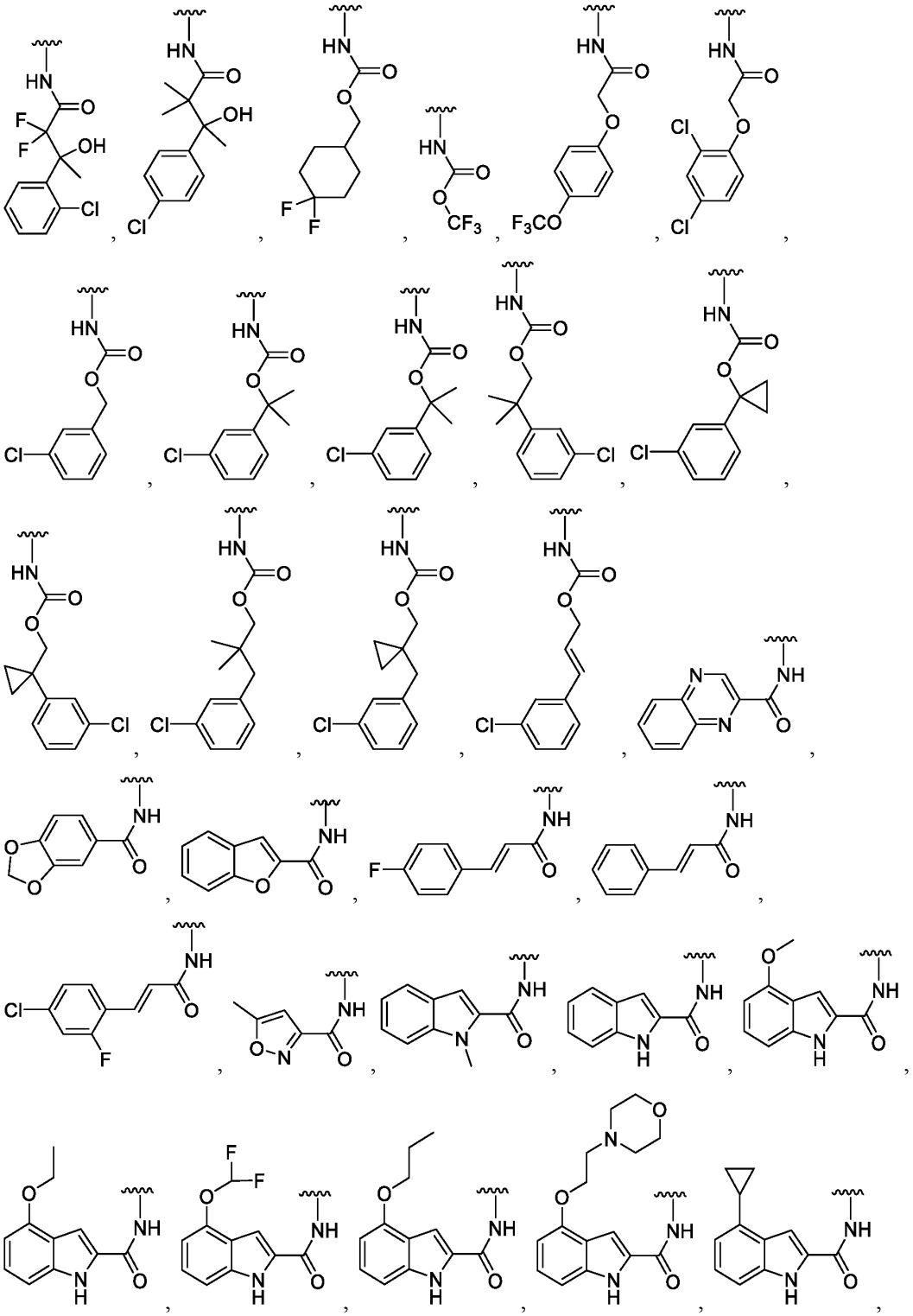
, and .

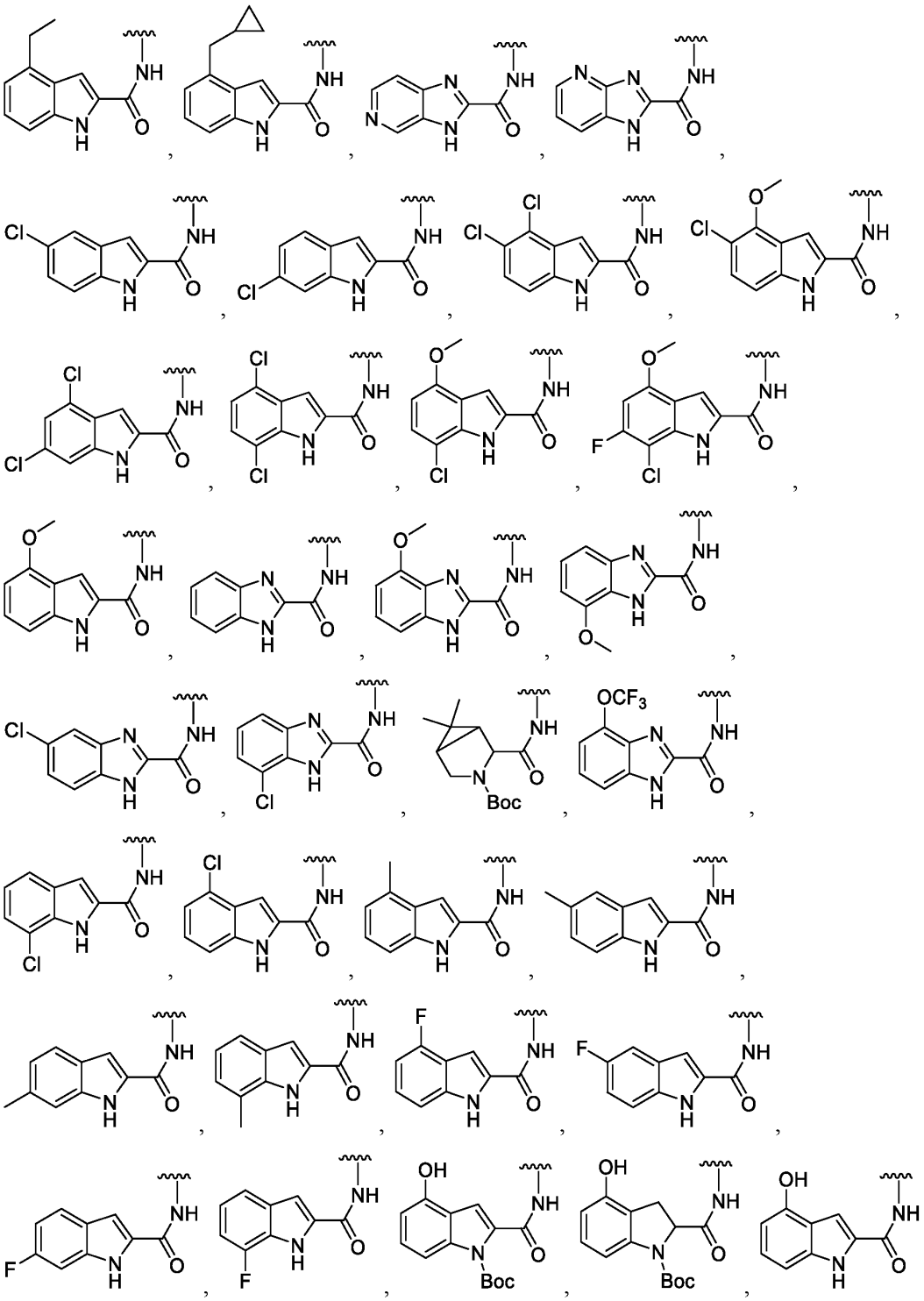
[000102] In various embodiments, R^2 is –NHC(O)R^B. In various embodiments, R^B is a 5-10 membered heteroaryl. In various embodiments, R^B is a bicyclic heteroaryl (e.g. 9 membered heteroaryl). In various embodiments, R^B is substituted. In various embodiments, R^B is unsubstituted. In various embodiments, R^B is substituted by halogen. In various embodiments, R^B is substituted by -OCH_3. In various embodiments, R^B is substituted by -OH. In various embodiments, R^B is substituted by C_1-C_8alkyl. In various embodiments, R^B is substituted by C_1-C_8alkoxy. In various embodiments, R^2 is substituted. In various embodiments, R^2 is unsubstituted. In various embodiments, R^2 is substituted by halogen. In various embodiments, R^2 is substituted by -OCH_3. In various embodiments, R^2 is substituted by -OH. In various embodiments, R^2 is substituted by C_1-C_8alkyl. In various embodiments, R^2 is substituted by C_1-C_8alkoxy.

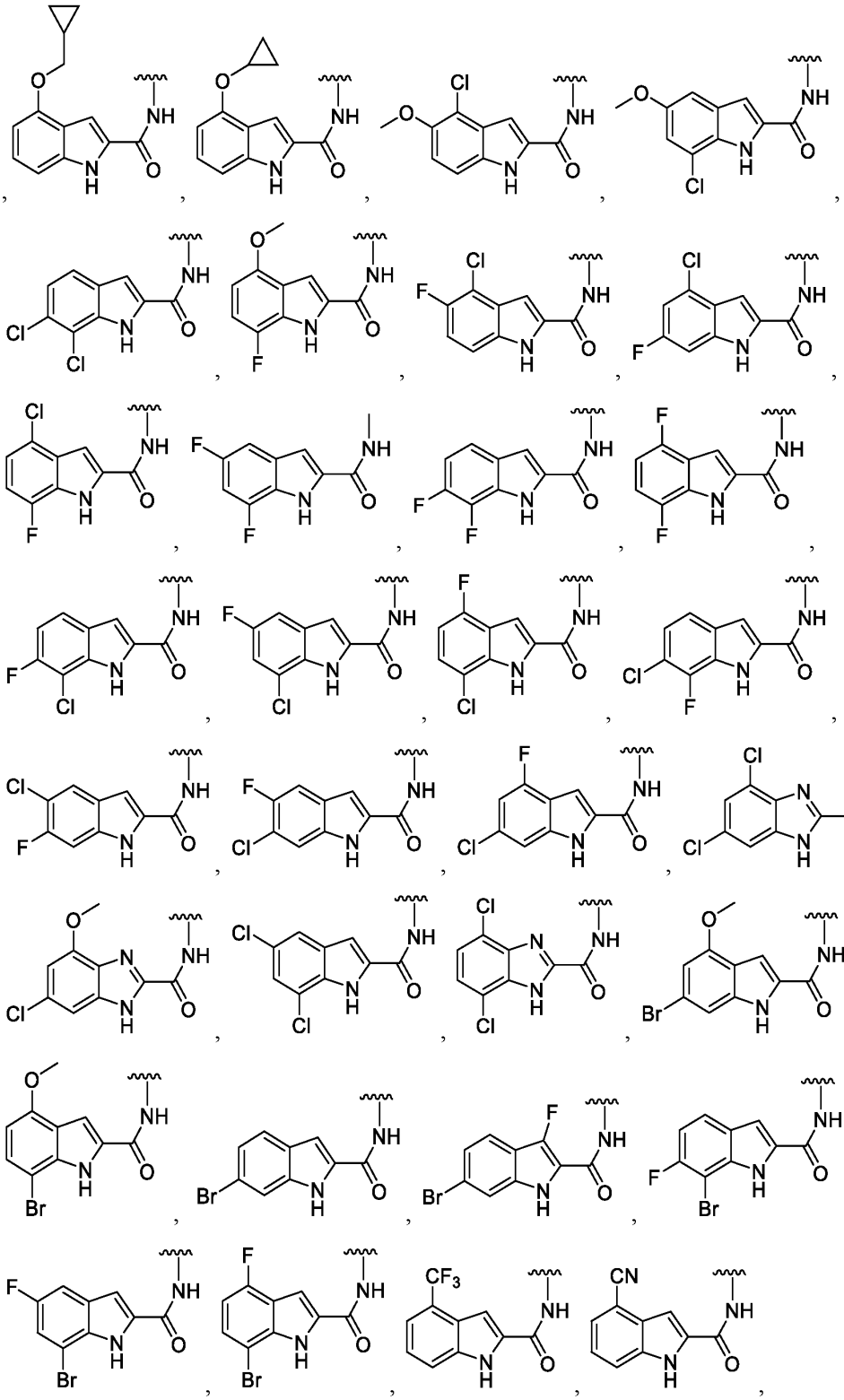
[000103] In some embodiments, R^2 is selected from the group consisting of

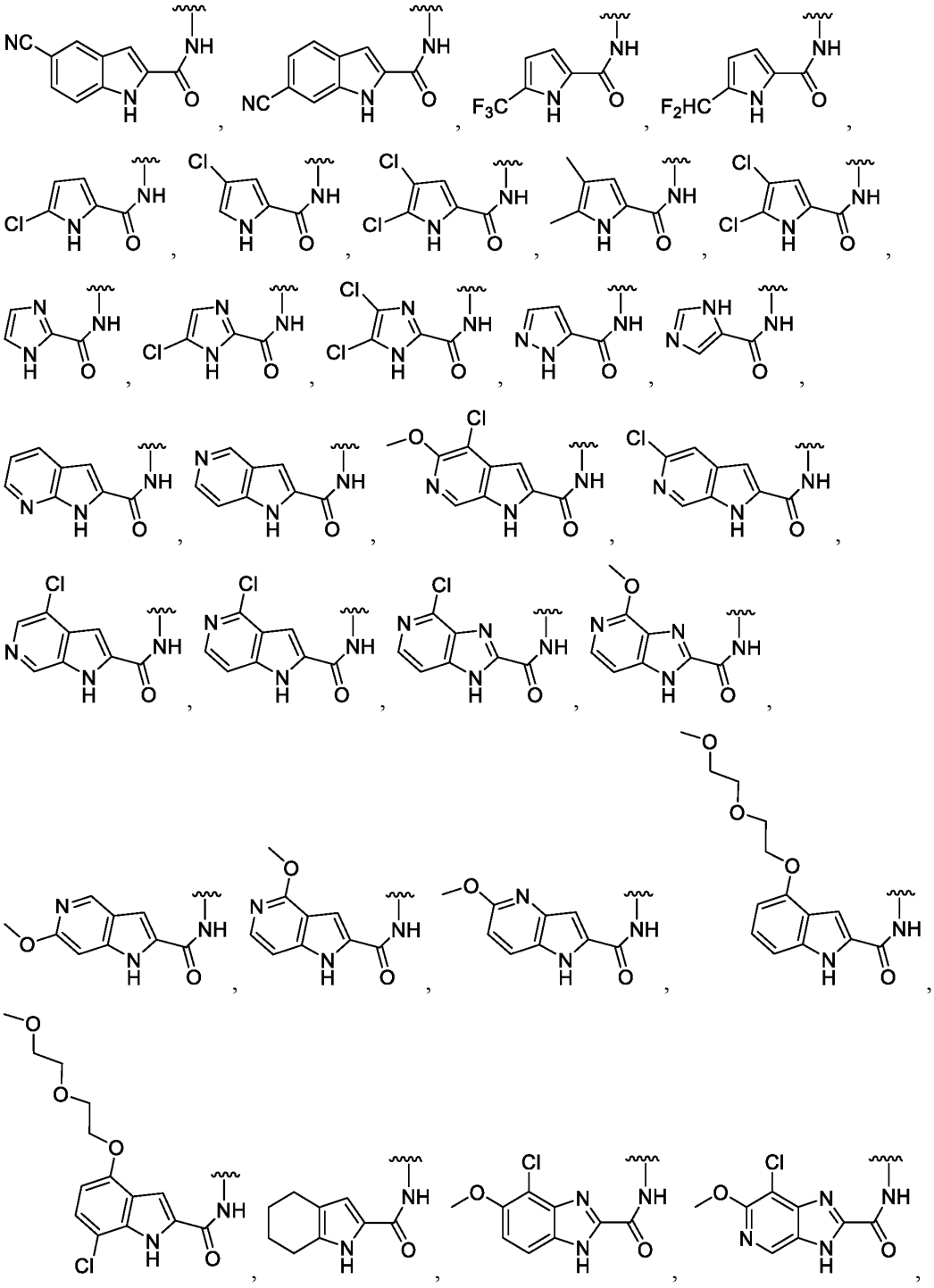


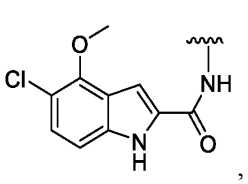
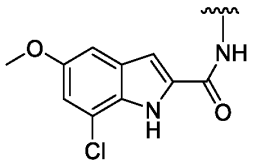
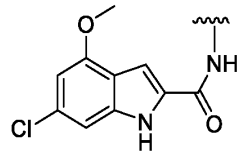
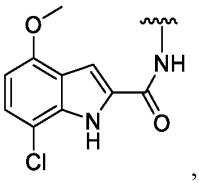
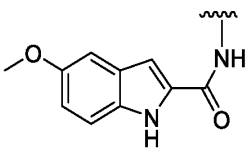
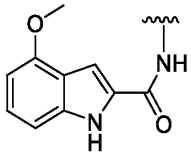
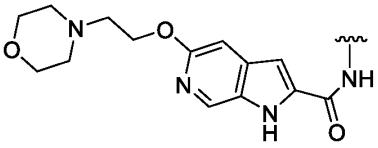
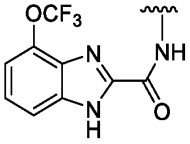


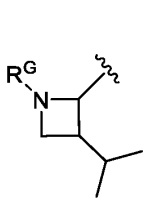
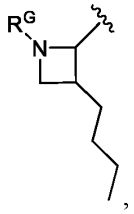
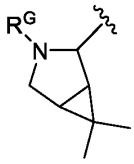
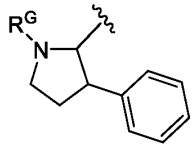
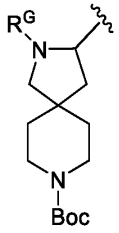
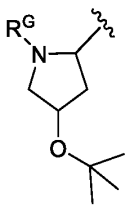
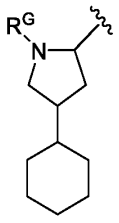
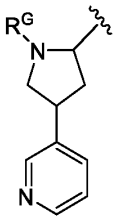
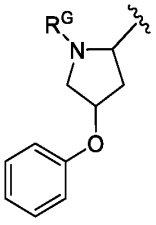
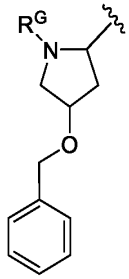
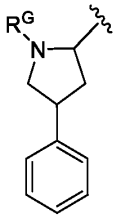
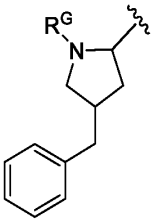
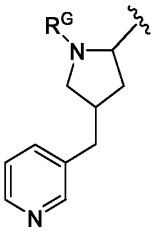
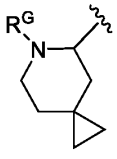
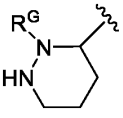




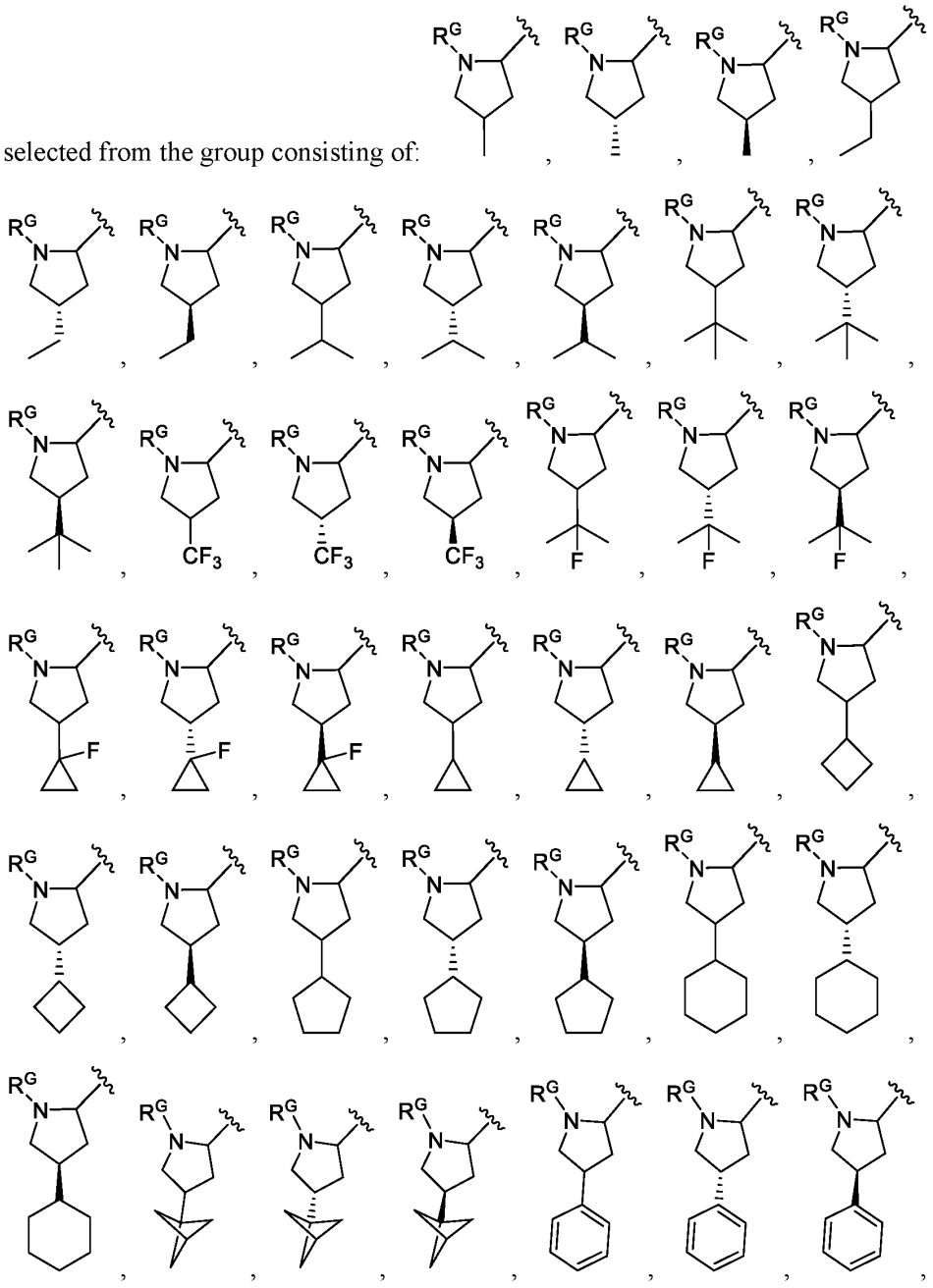


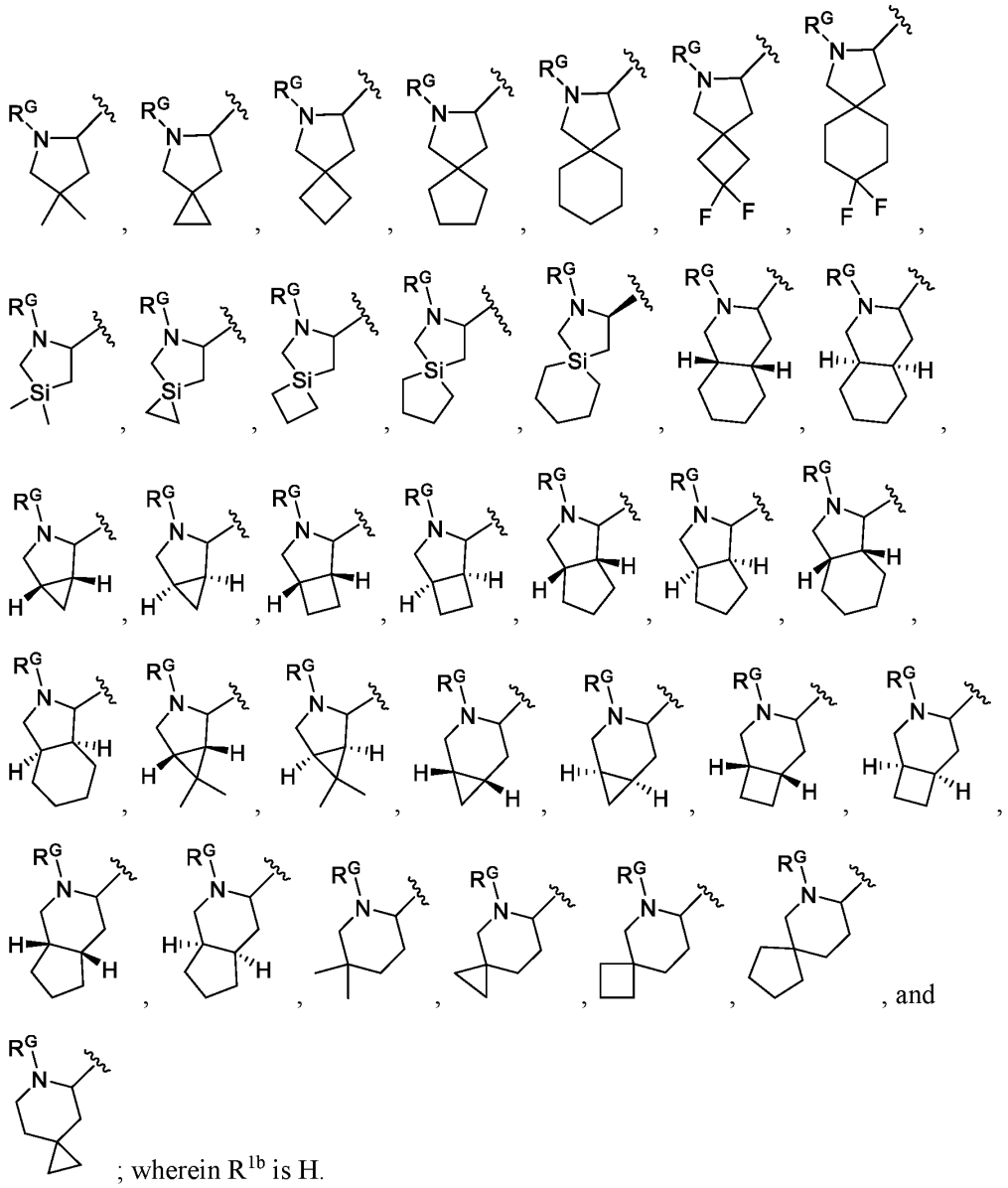



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[000104] In some embodiments, R^{1a} and R^2 are joined to together to form a heterocycle selected from the group consisting of:

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wherein R^{1b} is H.

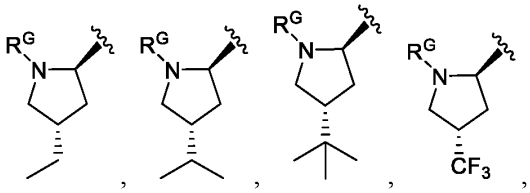
[000105] In some embodiments, R^{1a} and R^2 are joined to together to form a heterocycle selected from the group consisting of:

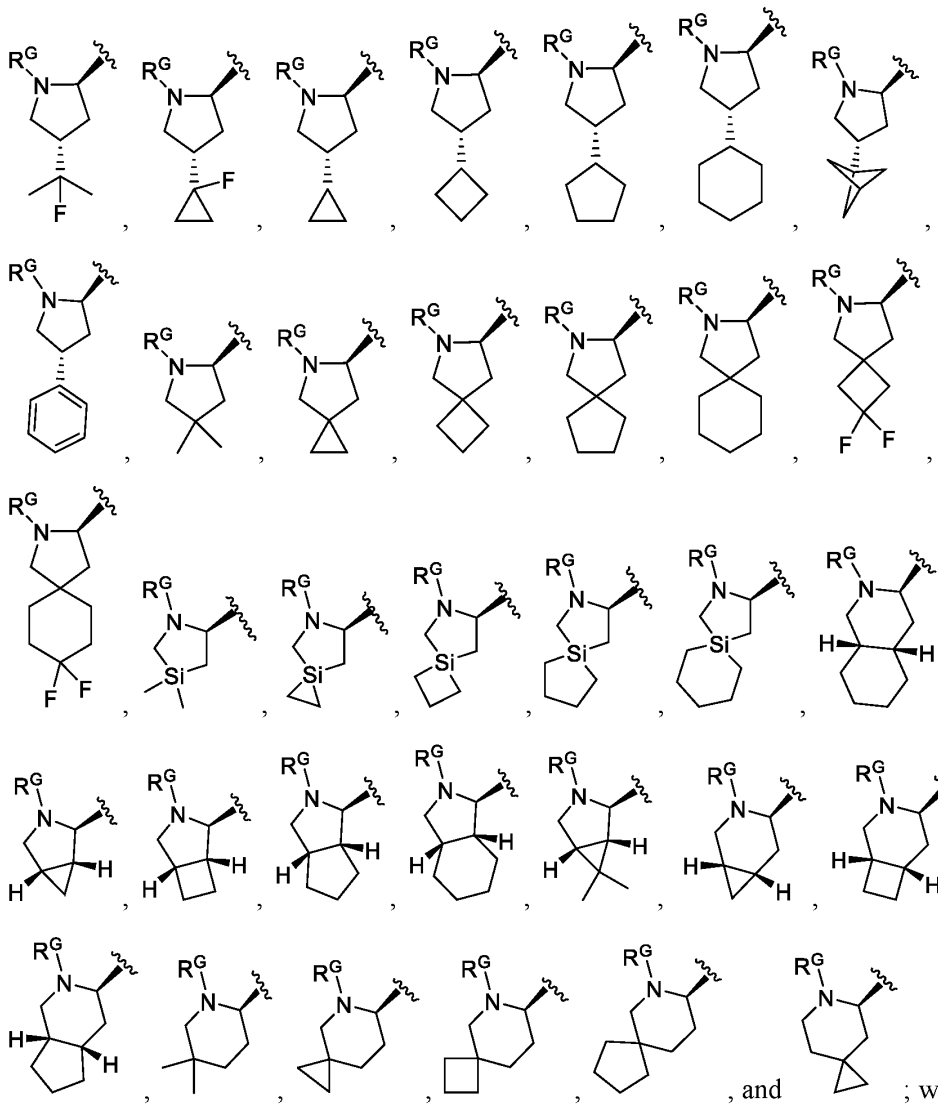




; wherein R^{1b} is H.

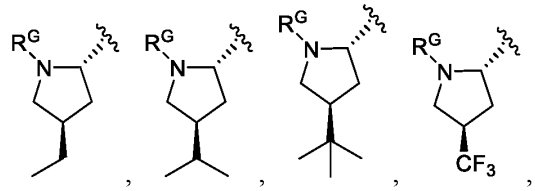
[000106] In some embodiments, R^{1a} and R^2 are joined to together to form a heterocycle selected from the group consisting of:

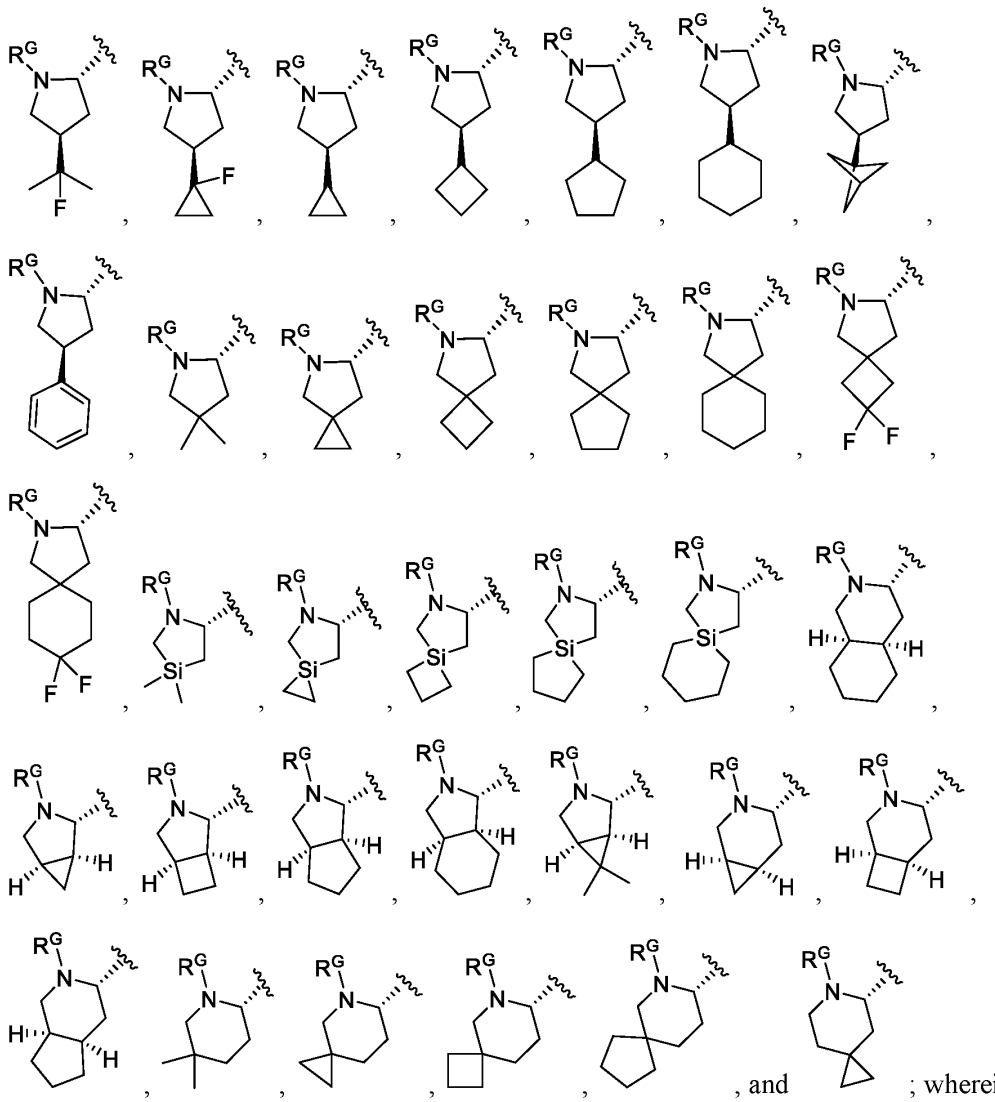




; wherein R^{1b} is H.

[00107] In some embodiments, R^{1a} and R^2 are joined to together to form a heterocycle selected from the group consisting of:





; wherein R^{1b} is H.

[000108] In some embodiments, R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-C_{3-6}cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{ii}.

[000109] In some embodiments, R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, and -C(=O)-C_{3-6}cycloalkyl.

[000110] In other embodiments, R^G is selected from the group consisting of –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{ii}.

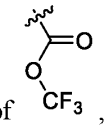
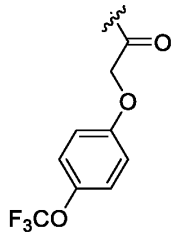
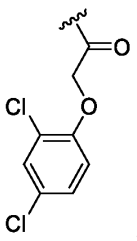
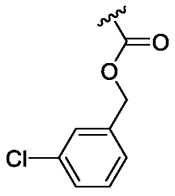
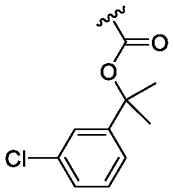
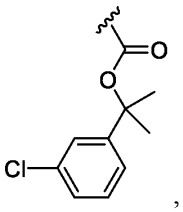
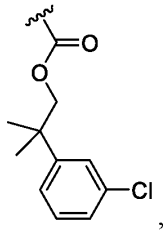
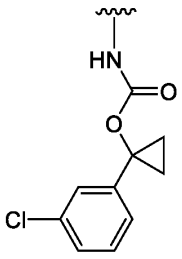
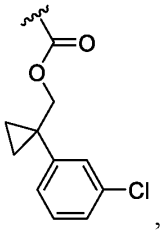
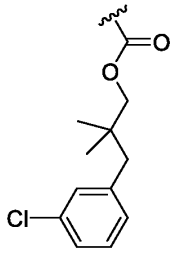
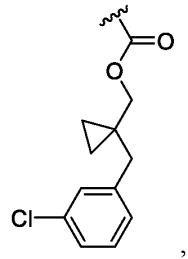
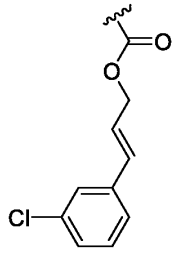
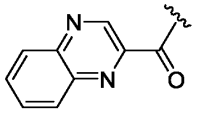
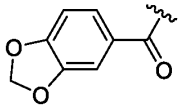
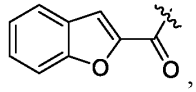
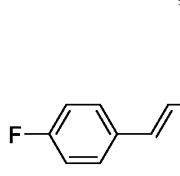
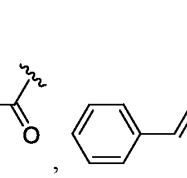
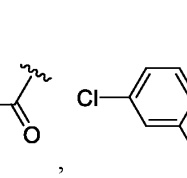
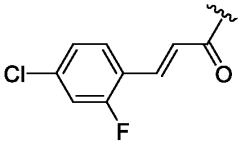
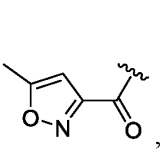
[000111] In some embodiments, R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m. In other embodiments, R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy. In further embodiments, R^{ii} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2.

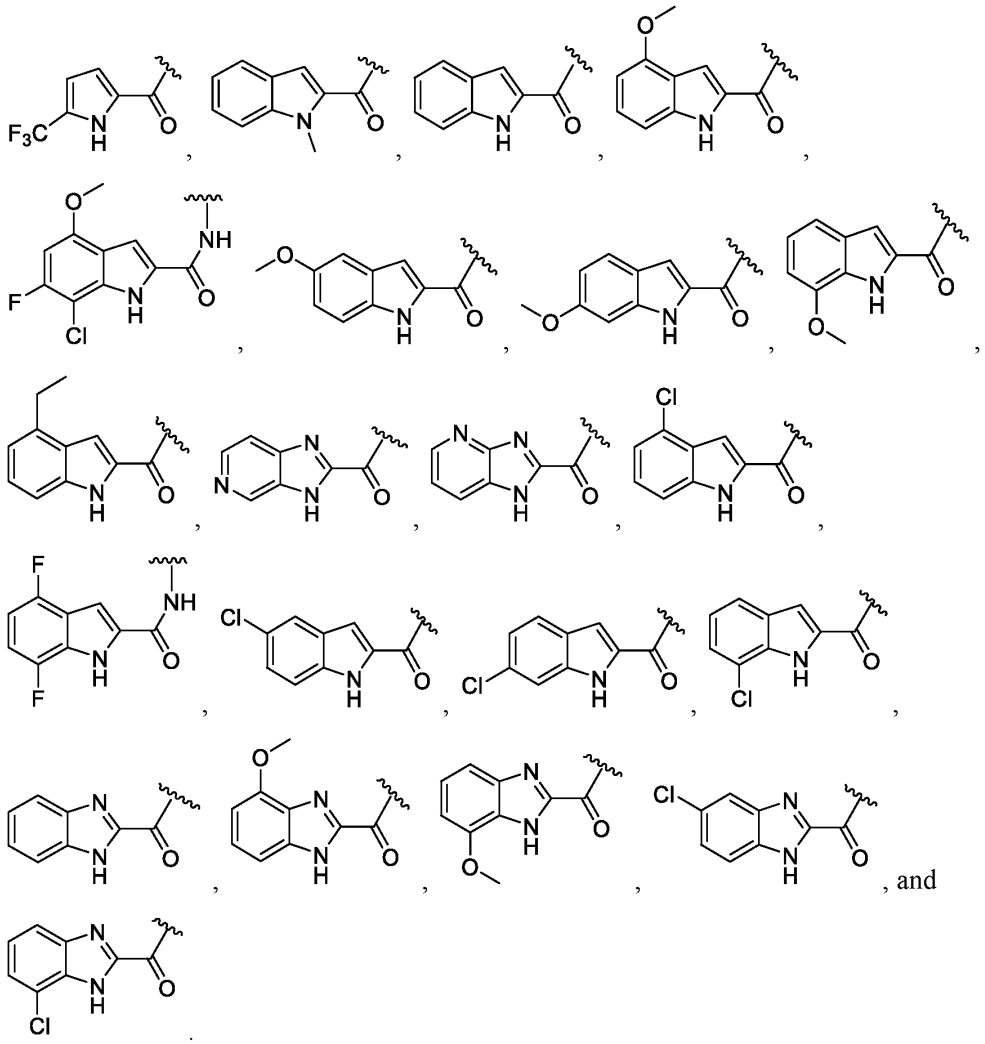
[000112] In certain embodiments, R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl (optionally substituted by one, two or three F), phenyl (optionally substituted by halo), -$S(O)_2$-CH_3, C_{3-6}cycloalkyl (optionally substituted by one, two, or three F), and 5-6 membered heteroaryl.

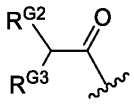
[000113] In some embodiments, R^G is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m) and C(=O)-C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl and heterocycle, wherein R^m is selected for each occurrence from H and C_{1-3}alkyl (optionally substituted by one, two or three halogens, e.g., F), or C_3-C_6cycloalkyl (optionally substituted by one, two, or three F).

[000114] In some embodiments, R^G is selected from the group consisting of a 5-6 membered monocyclic -C(O)-heteroaryl or an 8-10 membered bicyclic -C(O)-heteroaryl

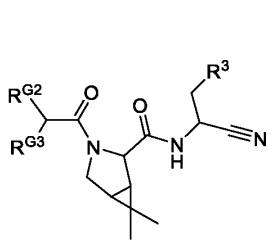
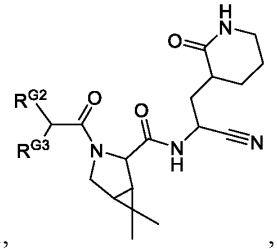
each having at least one ring nitrogen and optionally substituted by one, two, or three substituents each selected from halo, methoxy, cyano, and hydroxyl; and -C(O)-$C(R^{55}R^{56})$-NH-C(O)-R^{57}, wherein R^{55} is H and R^{56} is a straight or branched C_{1-5}alkyl (optionally substituted by halo), or R^{55} and R^{56} taken together with the carbon to which they are attached form a C_{3-5}cycloalkyl (optionally substituted by halo) and wherein R^{57} is C_{1-3}alkyl (optionally substituted by one, two or three halo).

[000115] In some embodiments, R^G is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 



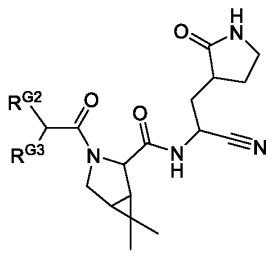
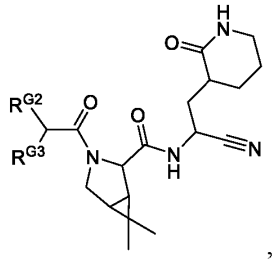
[000116] In some embodiments, R^G is  .

[000117] In some embodiments, a disclosed compound is represented by

 , e.g.,  , wherein R^{G3} is selected from the

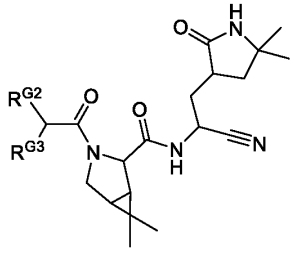
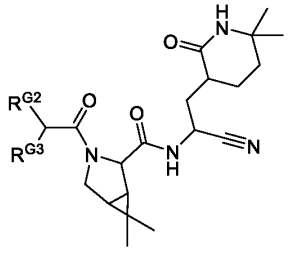
group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl (e.g., t-butyl, propyl, cyclopropyl), phenyl and heterocyclyl; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence from H, methyl and CF_3.

[000118] In some embodiments, a disclosed compound is represented by

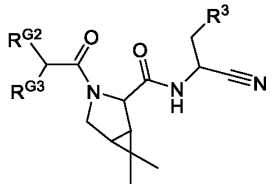
or , wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and heterocyclyl; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence from H, methyl and CF_3.

[000119] In some embodiments, a disclosed compound is represented by

or , wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and heterocyclyl; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence from H, methyl and CF_3.

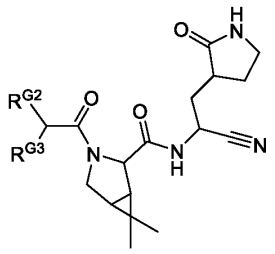
[000120] In some embodiments, a disclosed compound is represented by



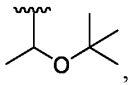
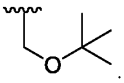
, wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three C_1-C_6alkoxy), C_{3-6}cycloalkyl, phenyl and heterocyclyl; and R^{G2} is selected from the group consisting of -NH(C_{1-3}alkyl) (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, optionally substituted phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl) and -NH(C=O)R^m, wherein R^m is selected for each

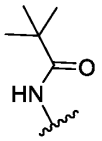
occurrence from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), CHF_2, CF_3, and 5-6 membered heteroaryl (optionally substituted by halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, CHF_2, or CF_3).

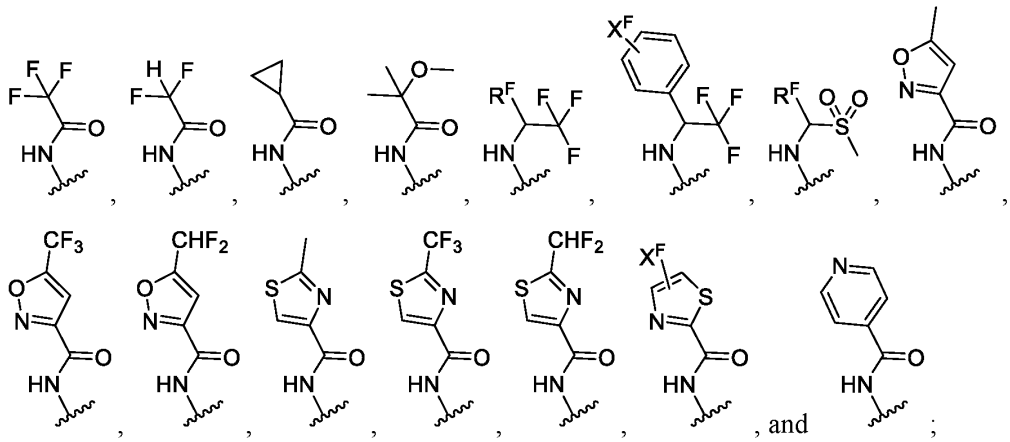
[000121] In some embodiments, a disclosed compound is represented by



, wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three C_1-C_6alkoxy), C_{3-6}cycloalkyl, phenyl and heterocyclyl; and R^{G2} is selected from the group consisting of -NH(C_{1-3}alkyl) (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, optionally substituted phenyl, -S(O)$_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl) and -NH(C=O)R^m, wherein R^m is selected for each occurrence from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), CHF_2, CF_3, and 5-6 membered heteroaryl (optionally substituted by halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, CHF_2, or CF_3).

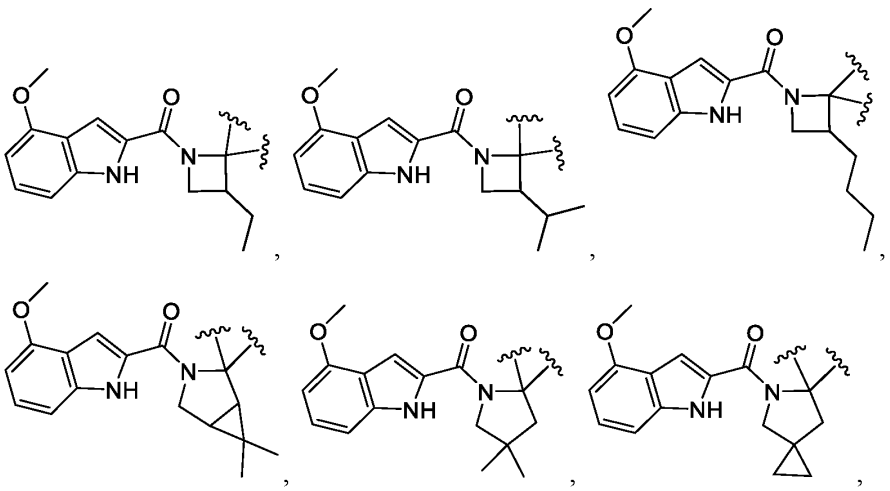
[000122] In some embodiments, R^{G3} is selected from the group consisting of  ,  ,  , and  .

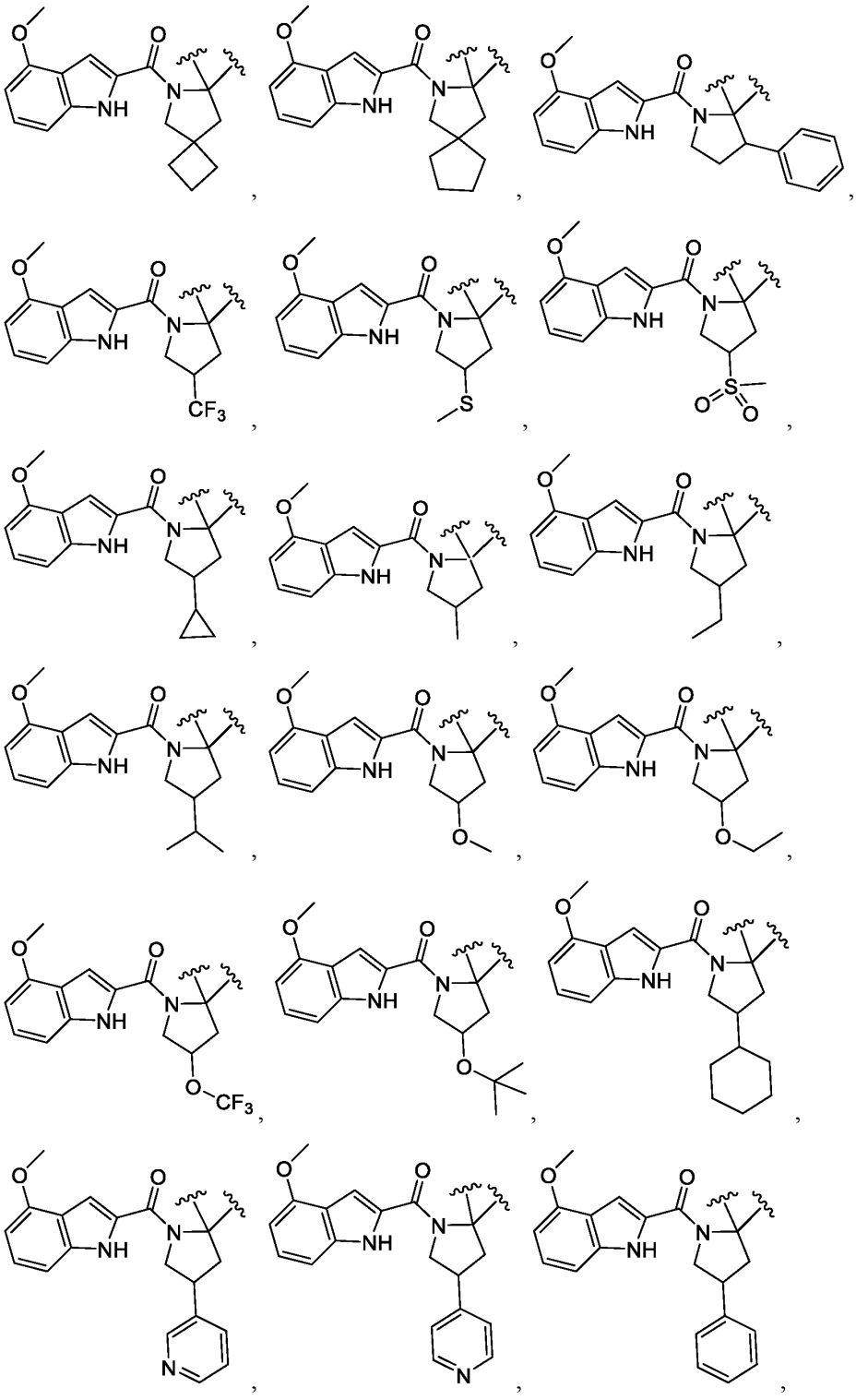
[000123] In some embodiments, R^{G2} is selected from the group consisting of  ,

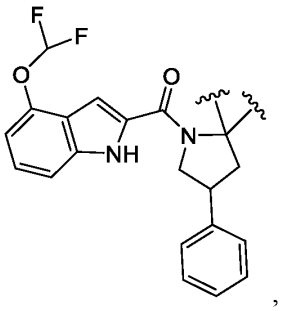
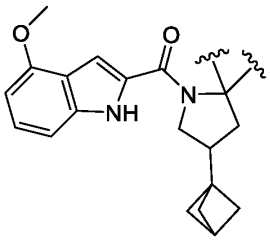
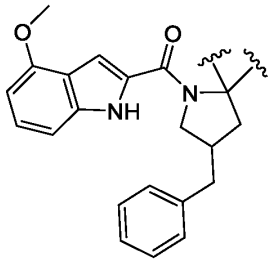
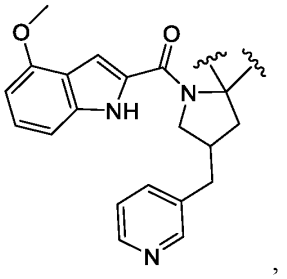
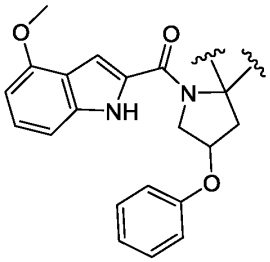
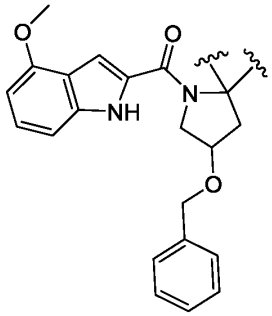
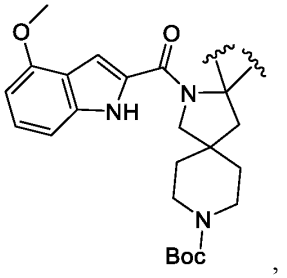
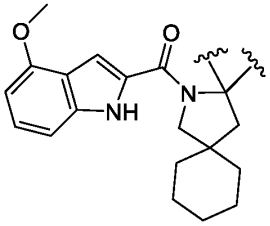
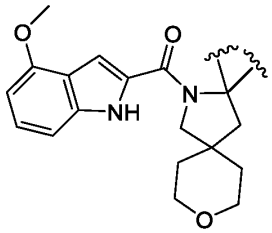
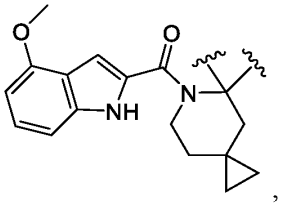
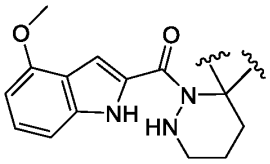
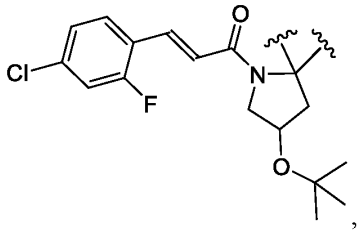
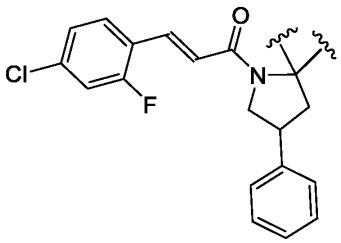
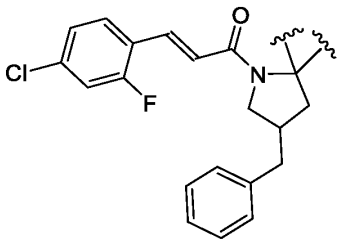
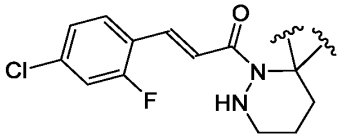


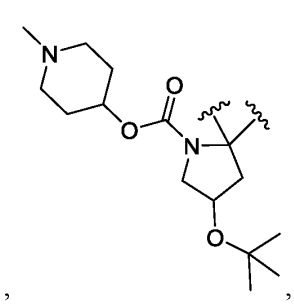
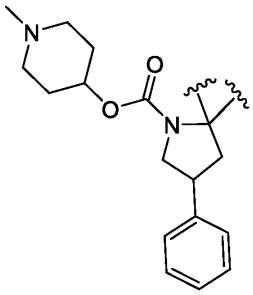
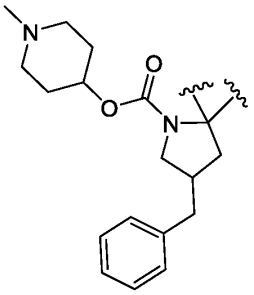
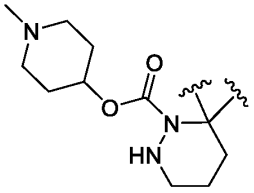
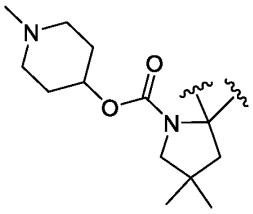
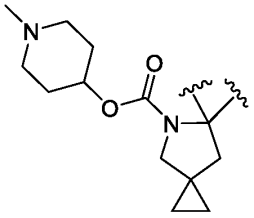
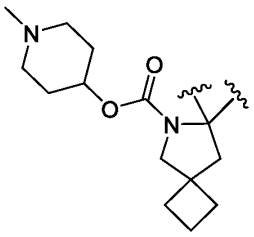
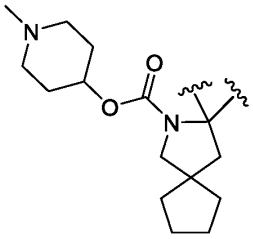
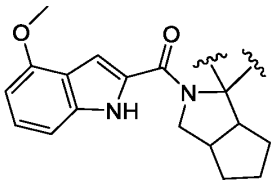
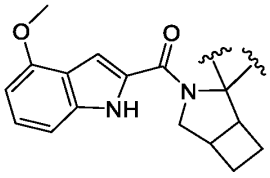
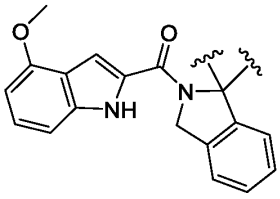
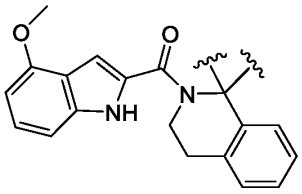
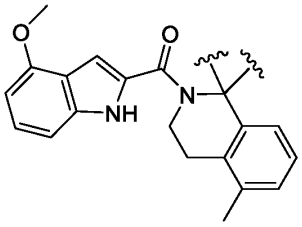
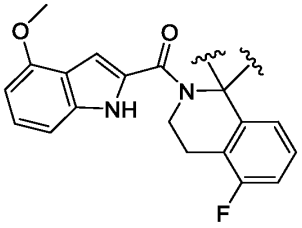
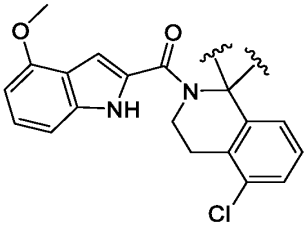
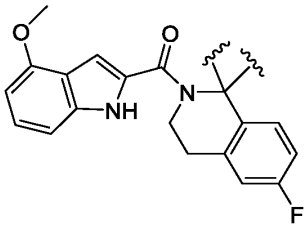
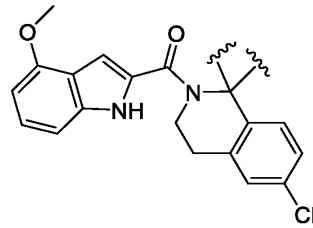
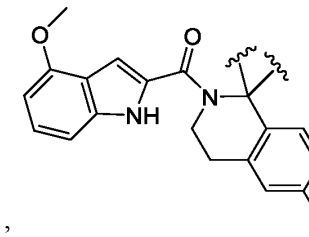
wherein R^F is selected from the group consisting of C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and 5-6 membered heteroaryl, wherein R^F may optionally be substituted by one, two or three substituents each selected from the group consisting of halo, cyano, hydroxyl and C_1-C_6alkoxy; and X^F is selected from the group consisting of H, halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, and C_{1-6}haloalkyl.

[000124] In some embodiments, R^{1a} and R^2 are joined to together to form a heterocycle selected from the group consisting of:





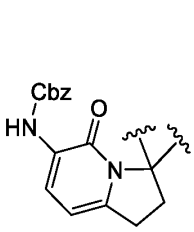
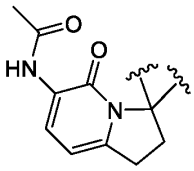
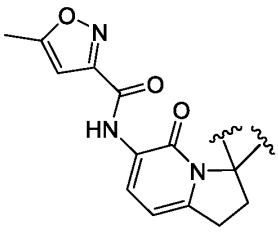
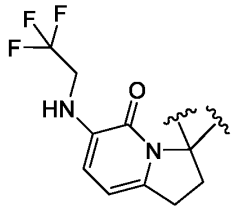
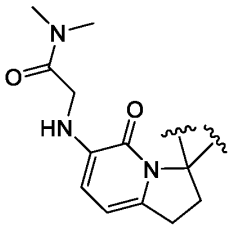
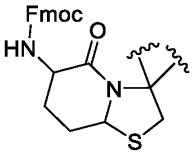
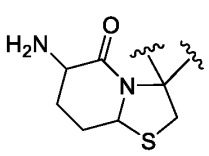
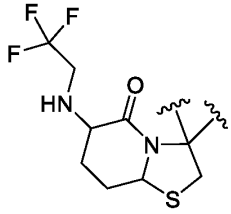
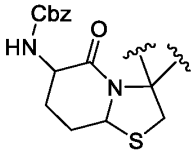
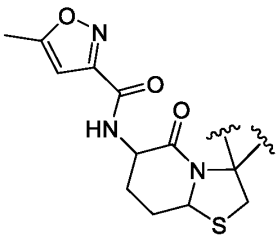
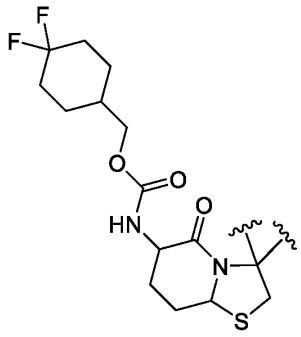
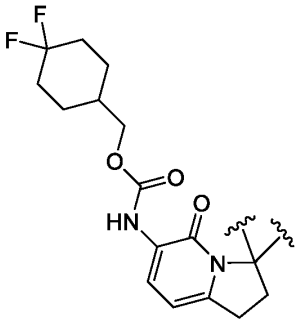
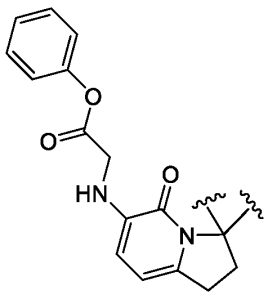
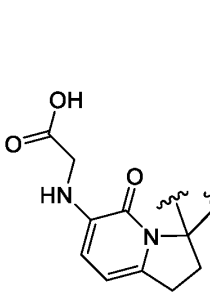
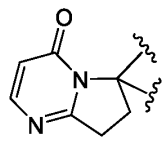

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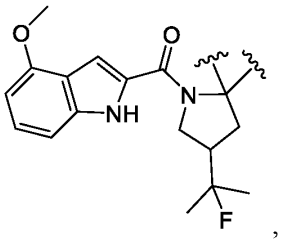
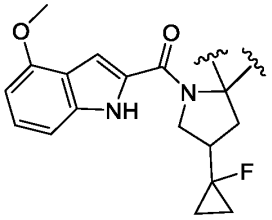
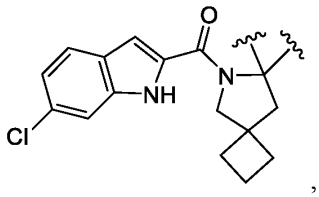
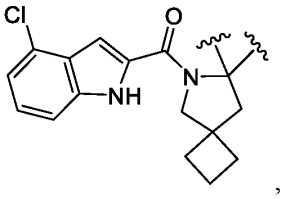
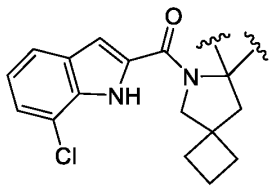
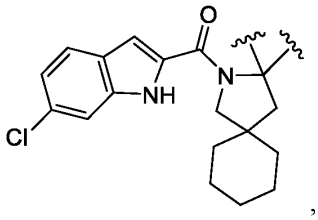
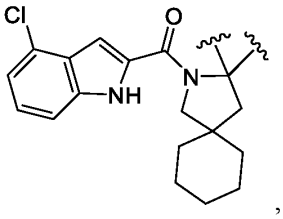
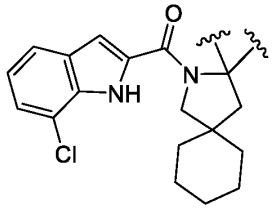
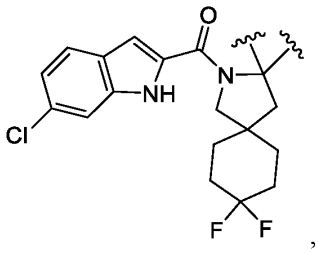
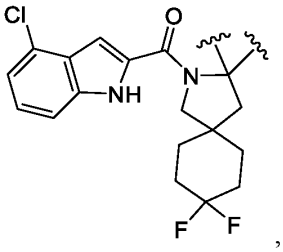
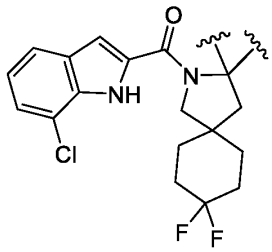
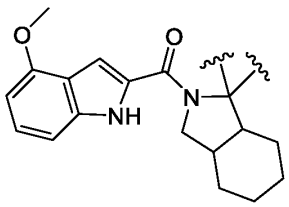
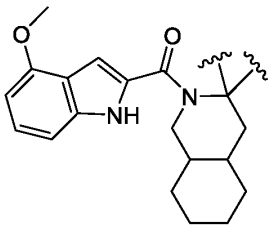
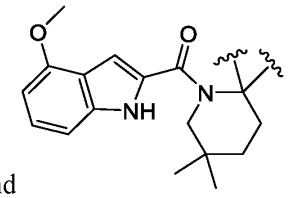

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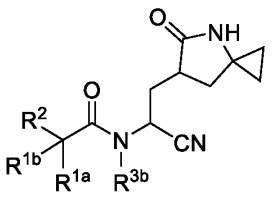
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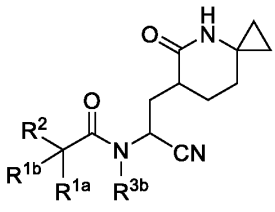

















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[000125] Further disclosed herein is a compound represented by Formula IV-A or Formula IV-B:



(IV-A) or



(IV-B)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen, NR^G, or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, –CH_2CF_3, –CF_3, –O-CF_3, –O-CHF_2, –S-CH_3, –$S(O)_2$-CH_3, –NH_2, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –$NHC(O)R^B$, –$NHC(O)OR^B$, –NHC(O)O-(C_1-C_8alkyl)-R^B, –$N(R^y)_2$, –$N(R^y)$(C_1-C_8alkyl)C(O)O-phenyl, –$N(R^y)$(C_1-C_8alkyl)$C(O)N(R^y)_2$, –C(O)-$OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, –NH_2, hydroxyl and oxo;

R^2 is selected from the group consisting of –NHC(O)R^B, –NHC(O)OR^B, –NHC(O)N(R^B)$_2$, –NHC(O)C(R^C)$_2$$R^B$, –NHS(O)$_2$$R^B$, –O-($C_1$-$C_8$alkyl)-($C_3$-$C_{10}$cycloalkyl), 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered monocyclic or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, -O-C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and

wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl;

R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-C_{3-6}cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{ii};

R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m;

R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy;

R^{ii} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2;

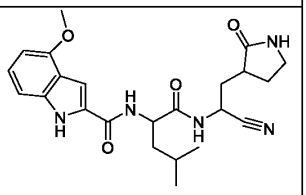
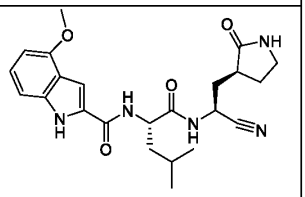
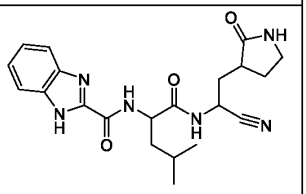
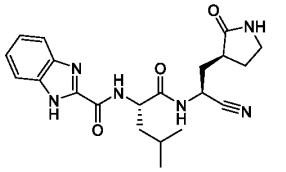
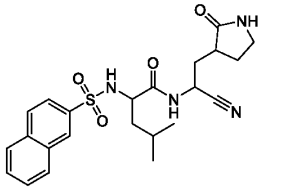
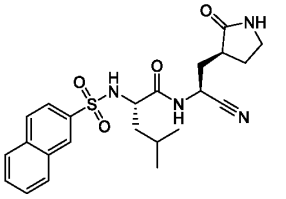
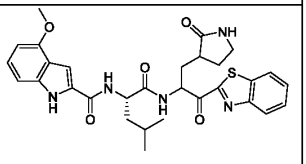
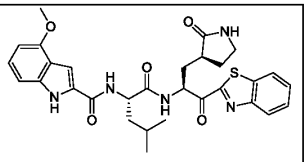
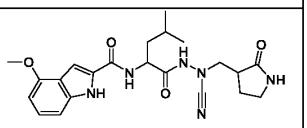
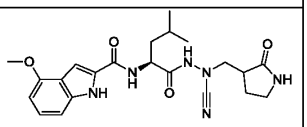
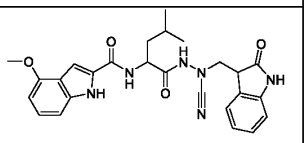
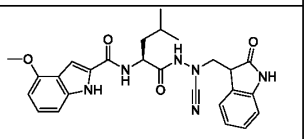
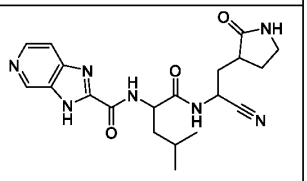
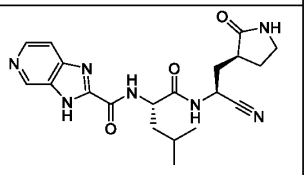
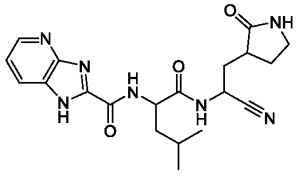
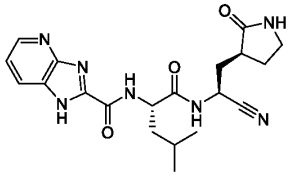
R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo;

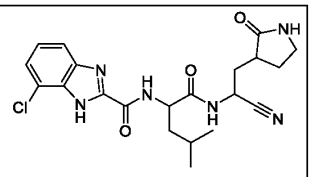
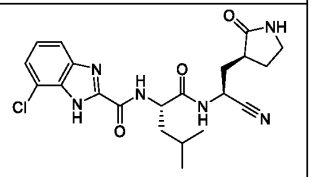
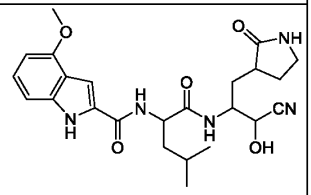
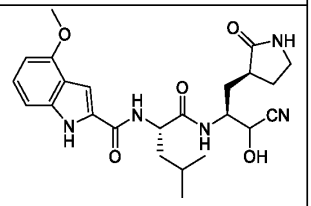
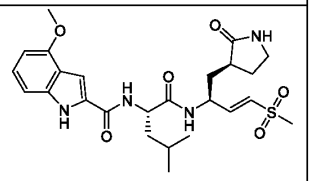
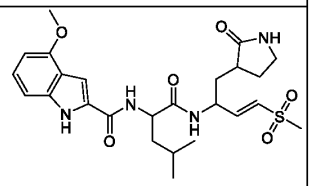
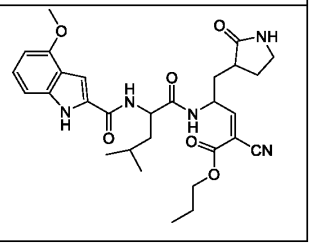
R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6; and

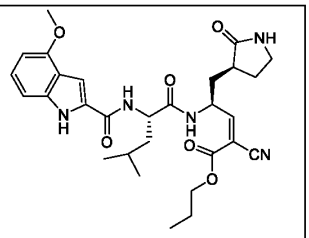
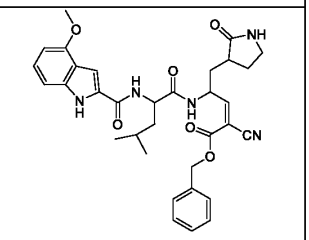
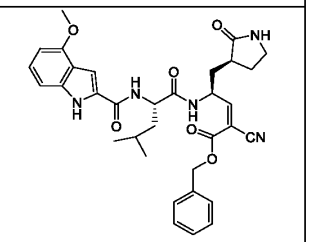
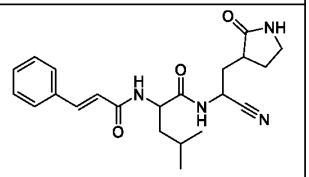
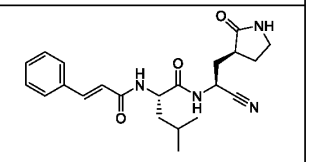
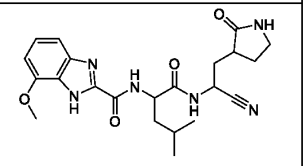
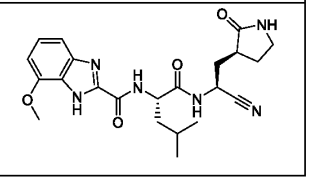
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), 5-10 membered heteroaryl, C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH.

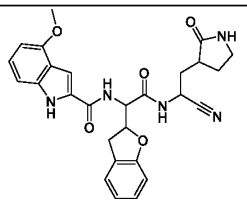
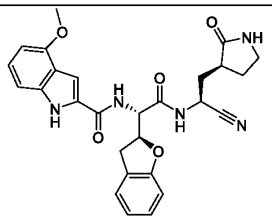
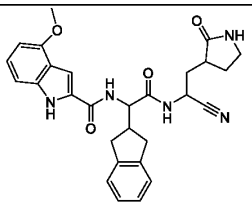
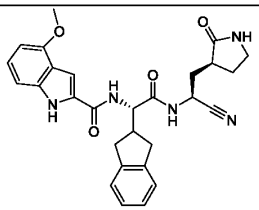
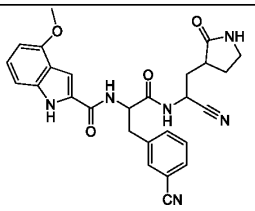
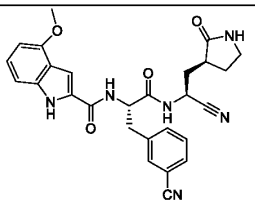
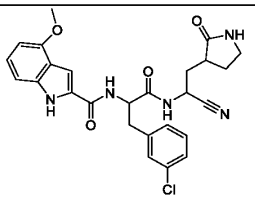
[000126] In some embodiments, a disclosed compound is selected from the group consisting of the compounds identified in Table 1 and Table 2 below:

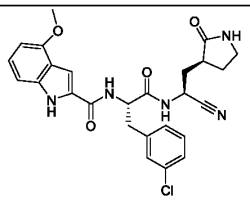
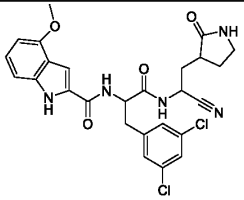
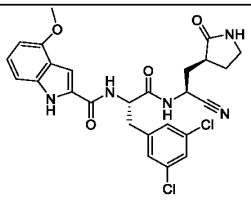
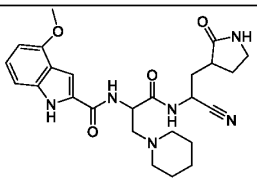
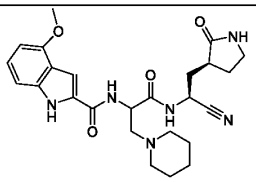
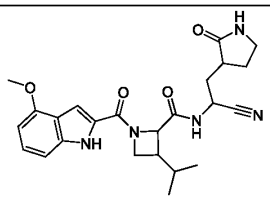
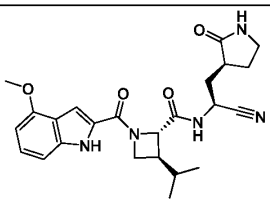
Table 1. Exemplary compounds.

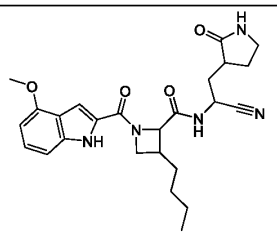
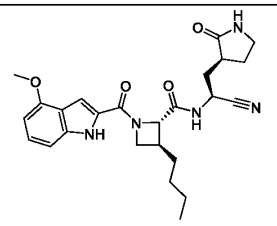
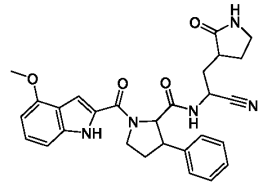
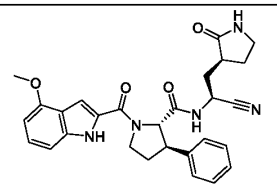
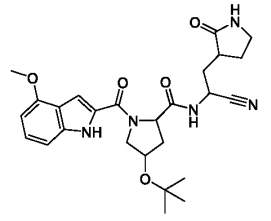
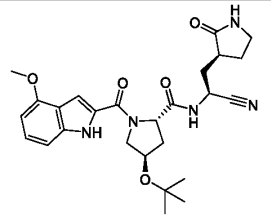
Cmpd No.	Structure
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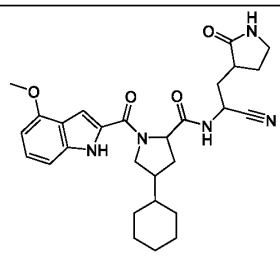
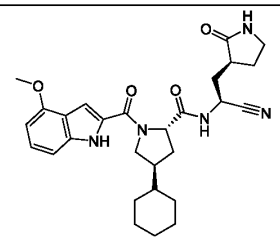
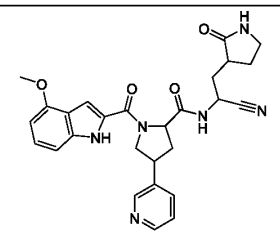
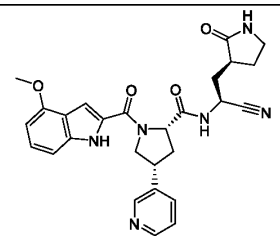
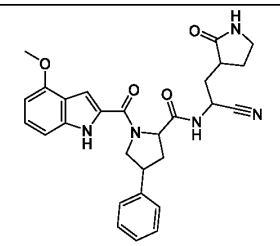
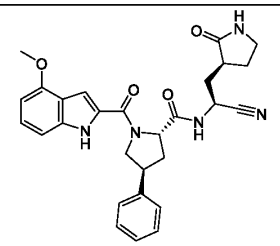
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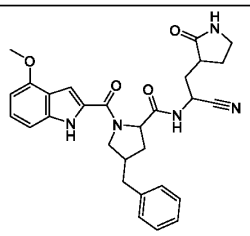
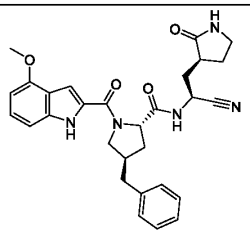
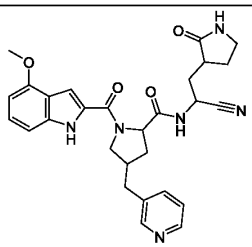
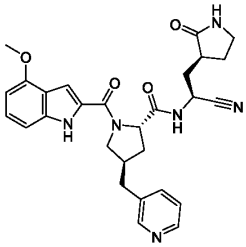
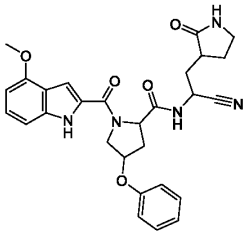
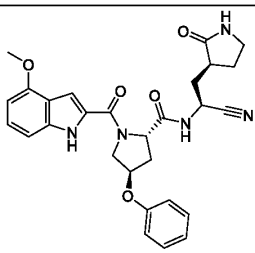
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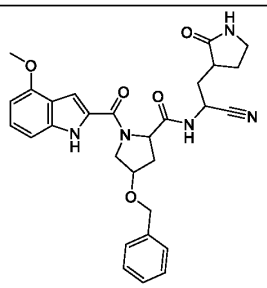
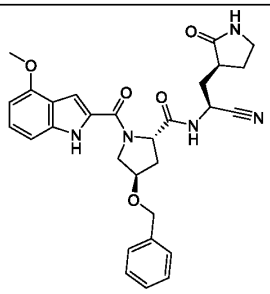
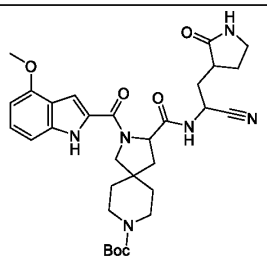
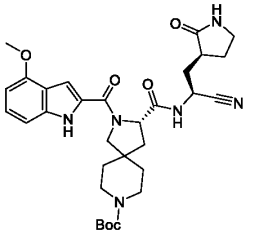
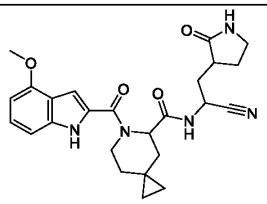
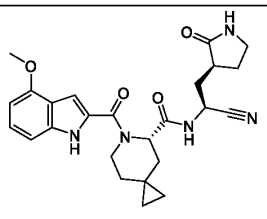
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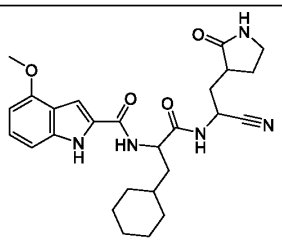
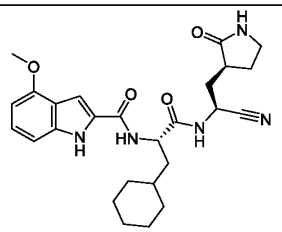
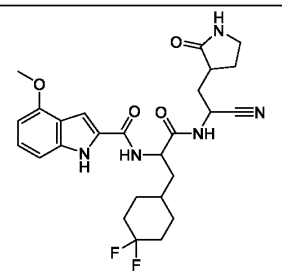
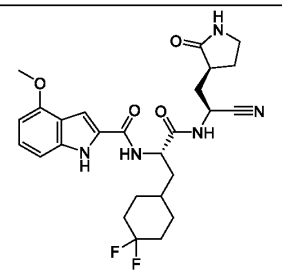
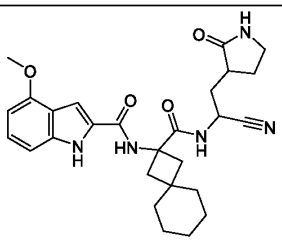
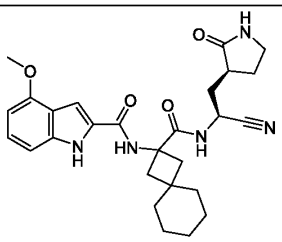
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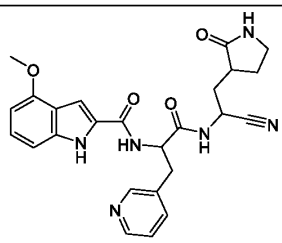
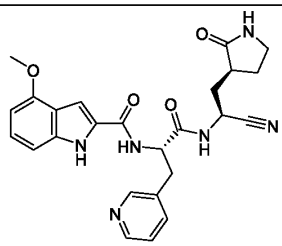
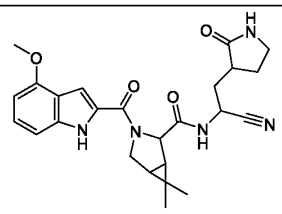
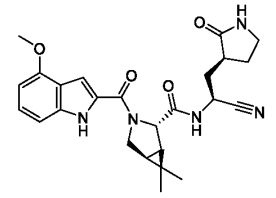
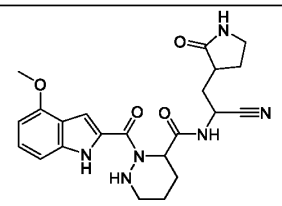
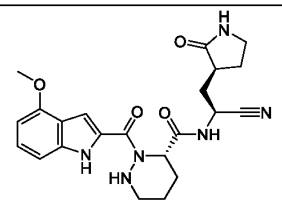
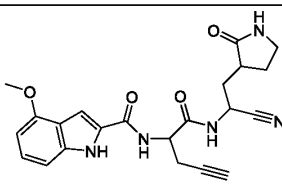
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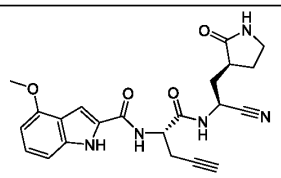
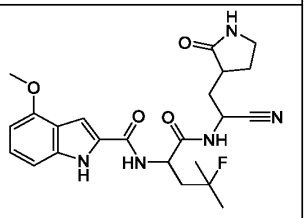
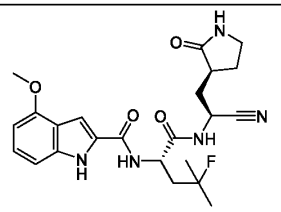
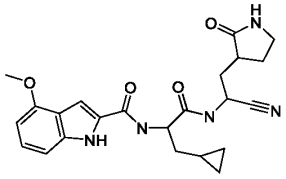
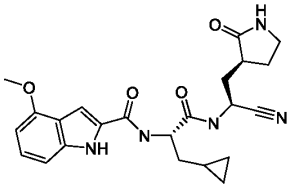
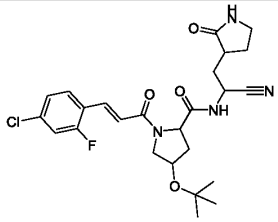
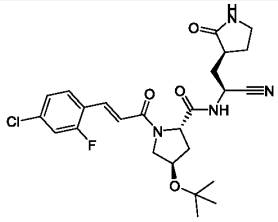
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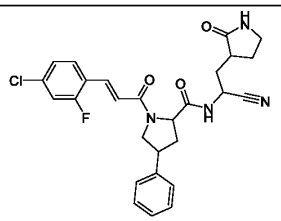
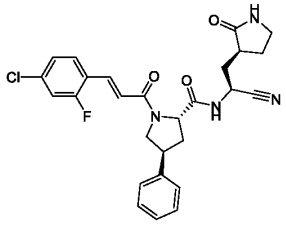
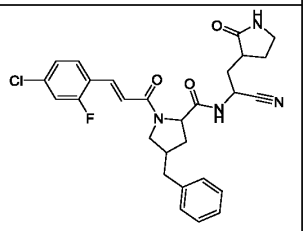
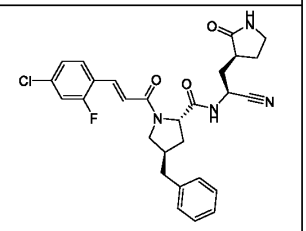
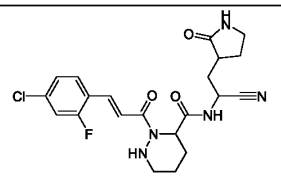
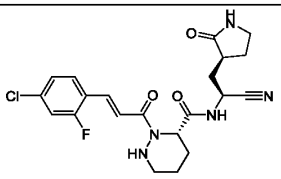
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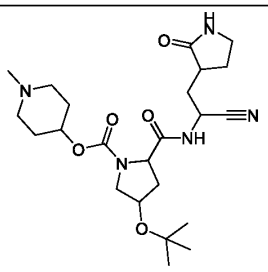
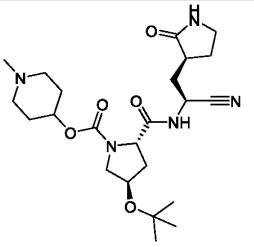
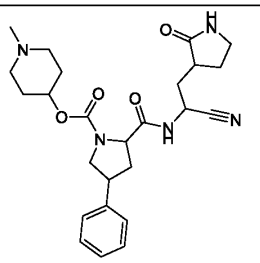
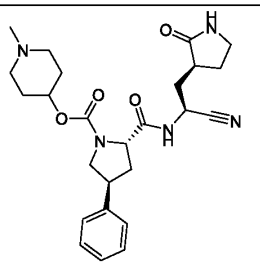
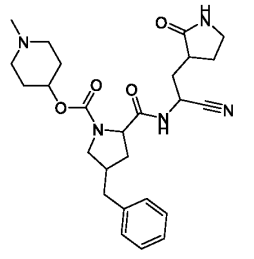
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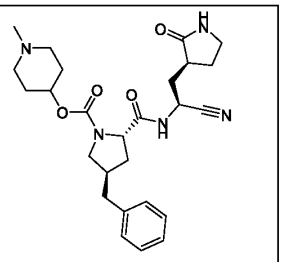
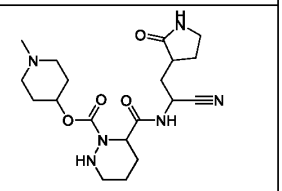
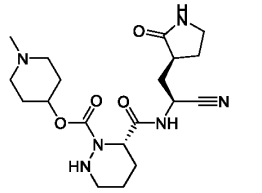
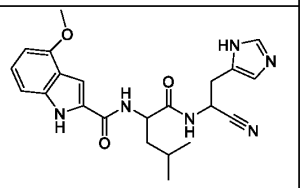
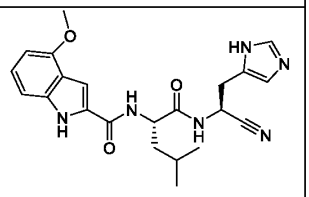
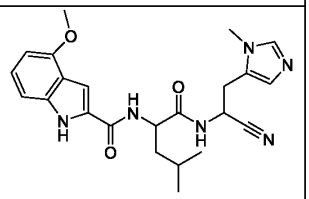
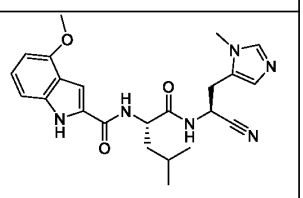
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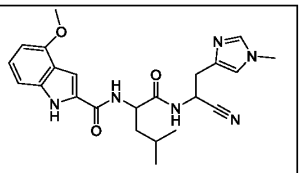
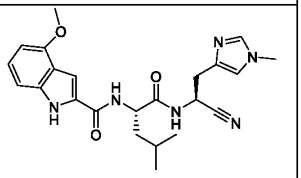
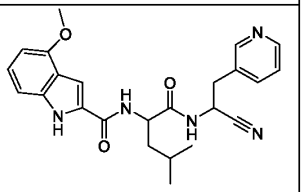
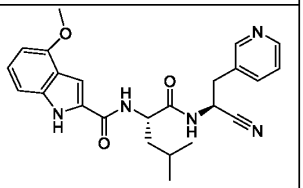
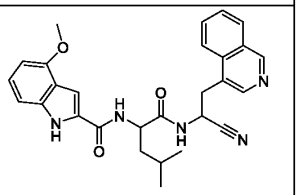
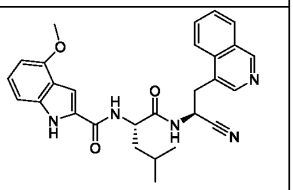
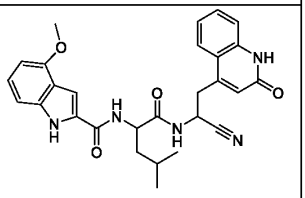
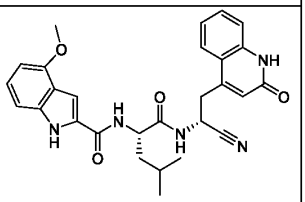
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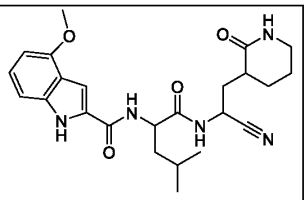
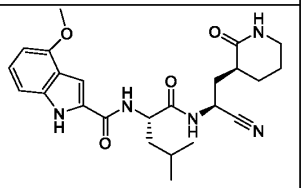
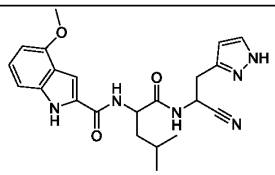
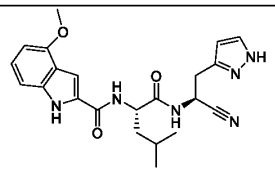
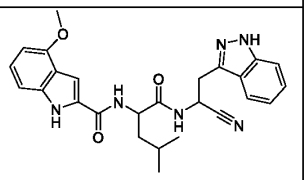
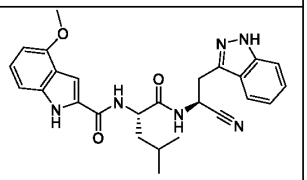
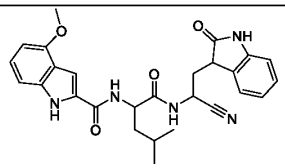
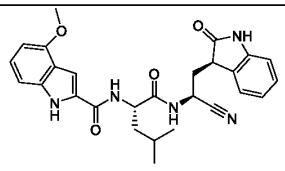
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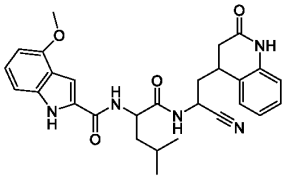
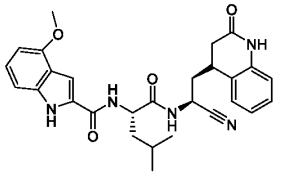
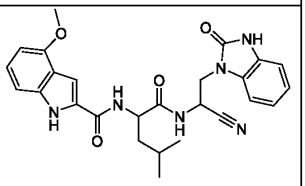
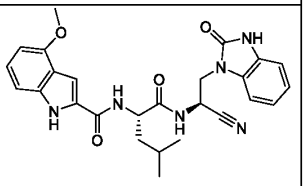
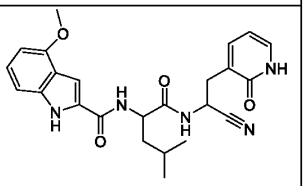
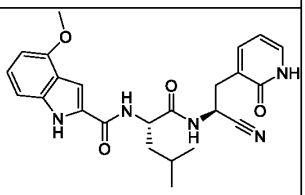
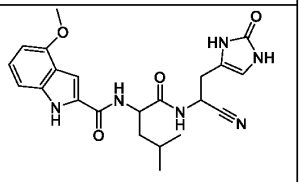
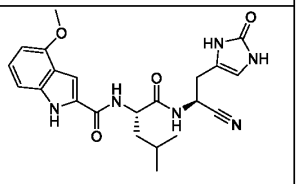
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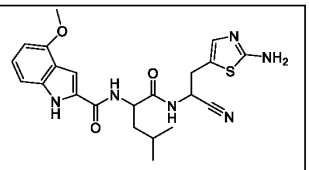
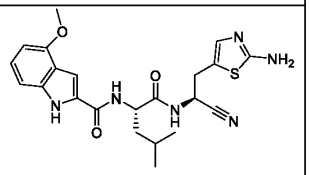
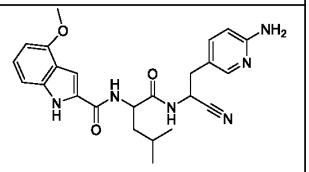
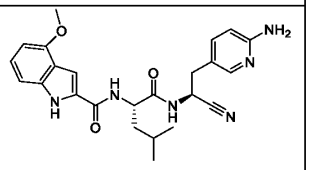
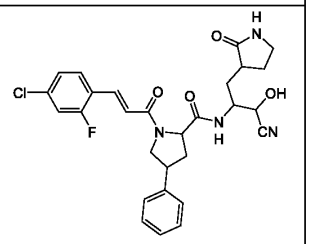
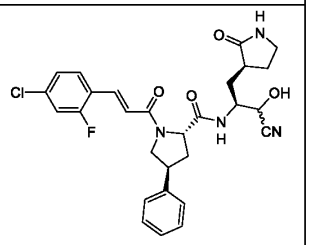
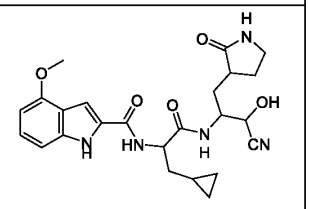
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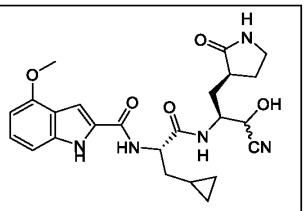
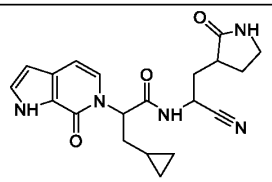
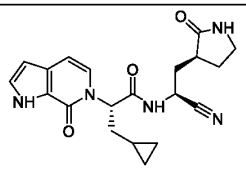
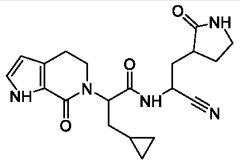
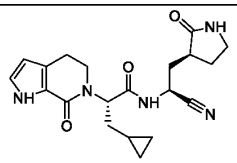
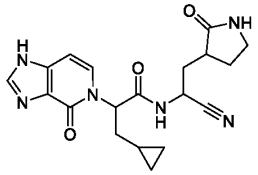
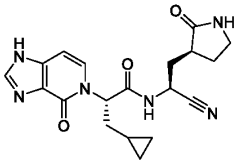
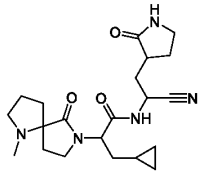
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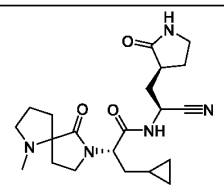
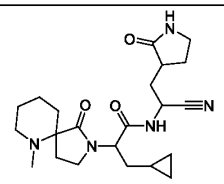
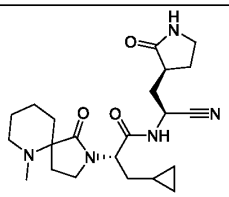
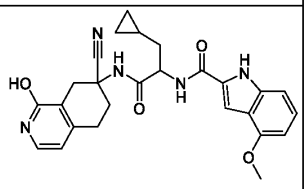
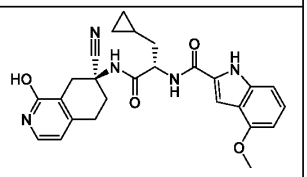
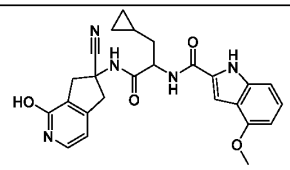
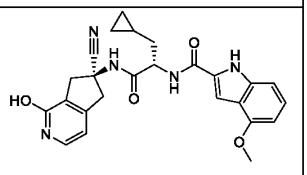
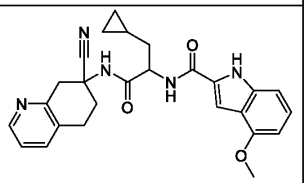
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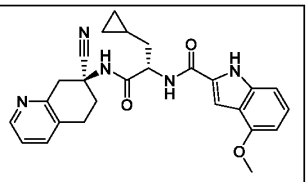
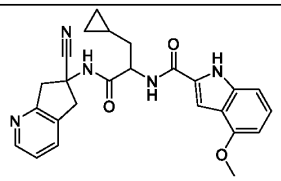
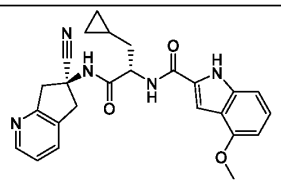
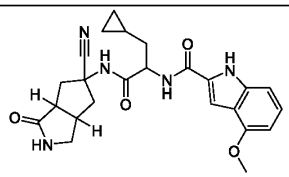
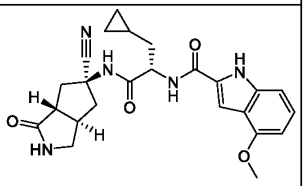
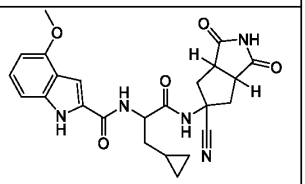
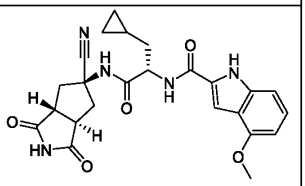
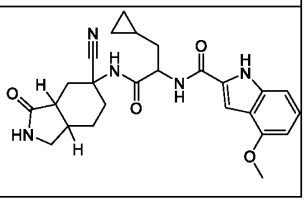
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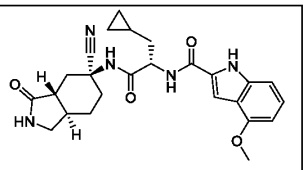
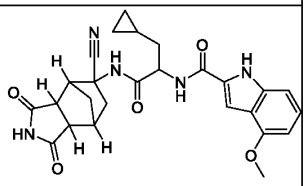
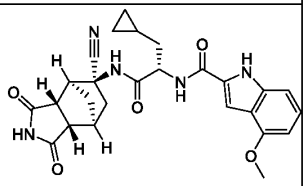
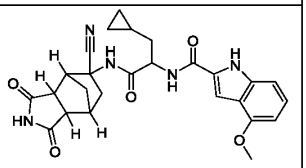
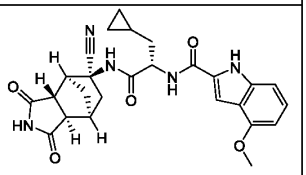
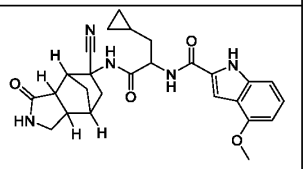
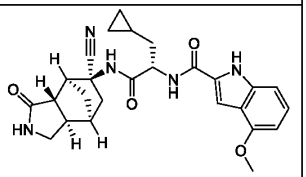
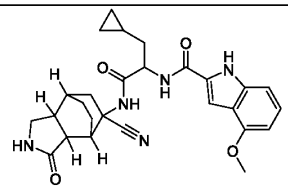
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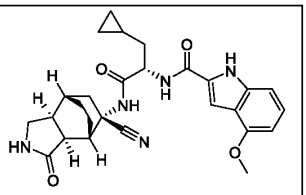
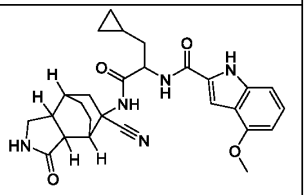
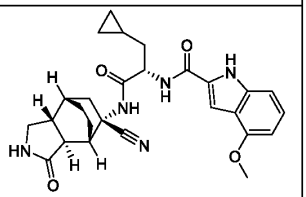
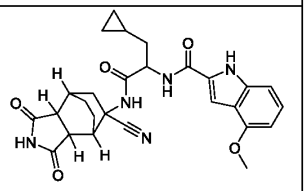
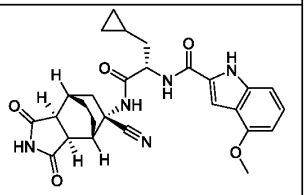
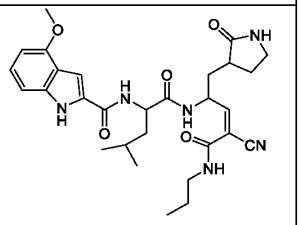
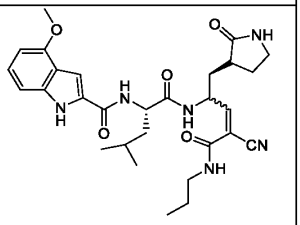
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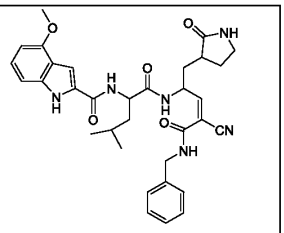
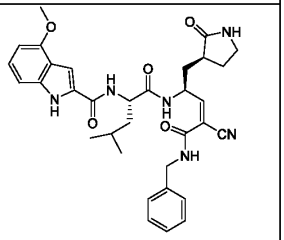
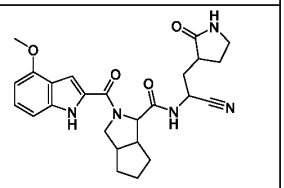
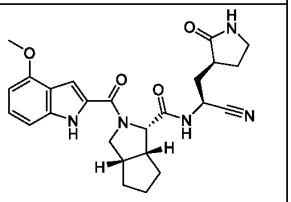
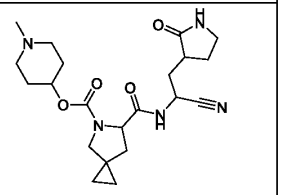
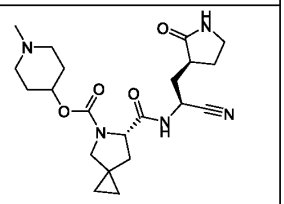
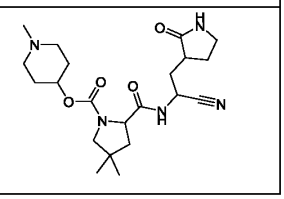
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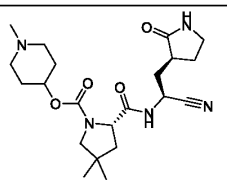
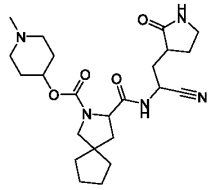
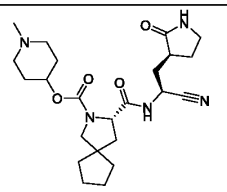
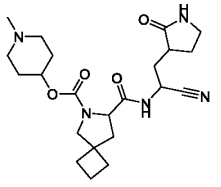
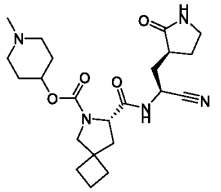
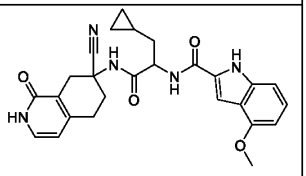
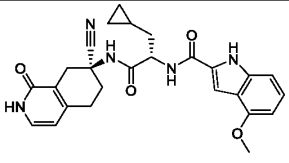
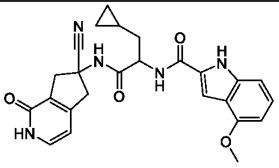
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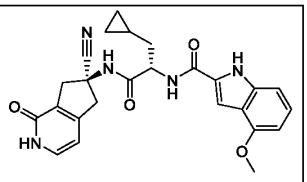
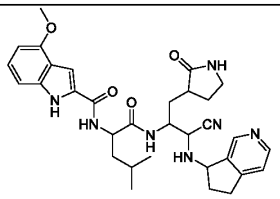
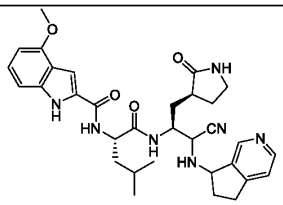
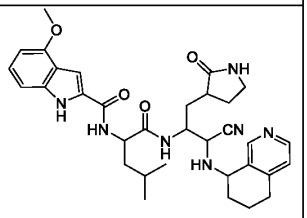
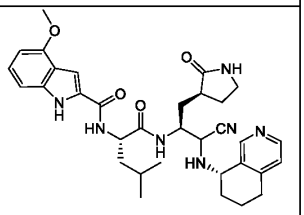
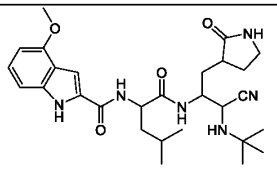
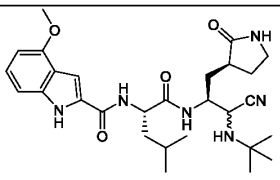
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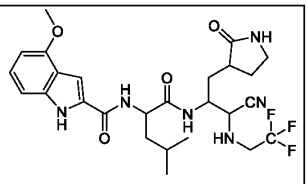
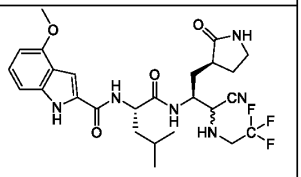
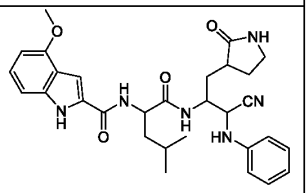
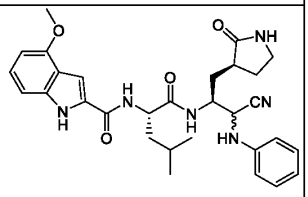
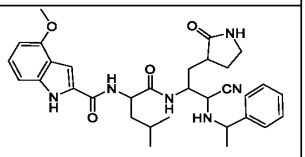
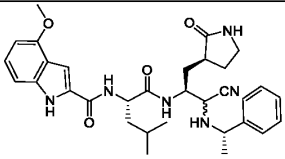
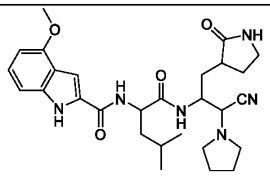
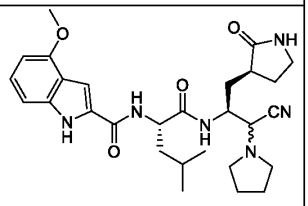
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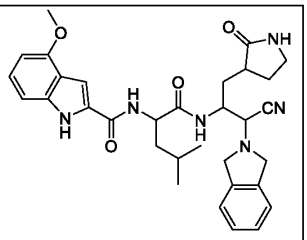
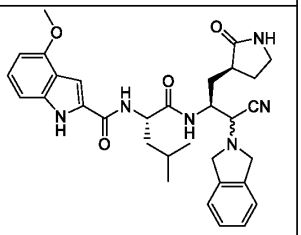
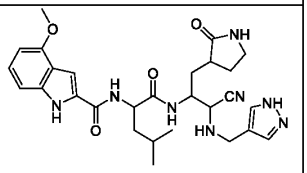
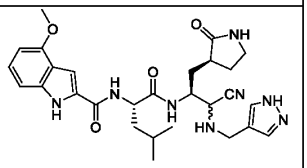
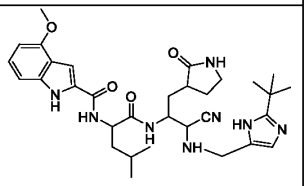
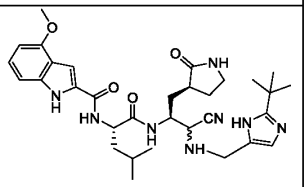
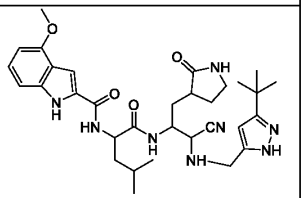
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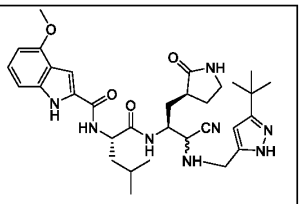
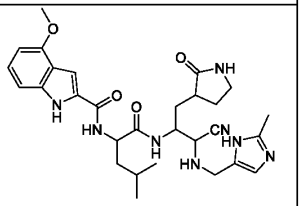
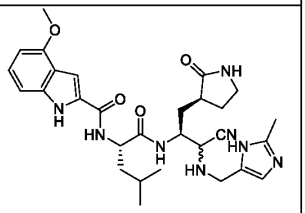
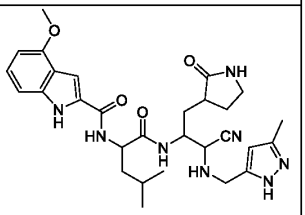
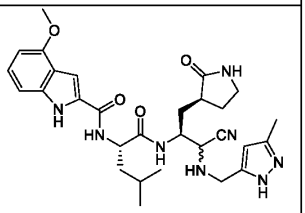
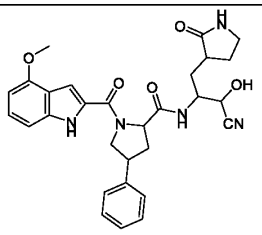
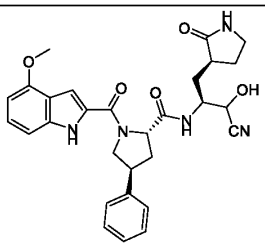
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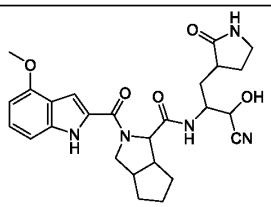
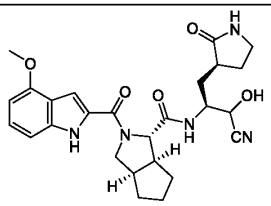
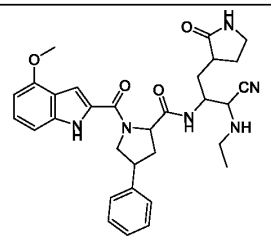
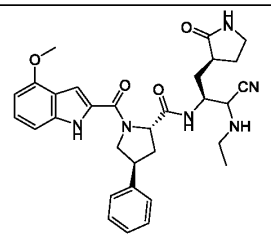
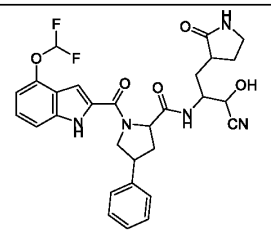
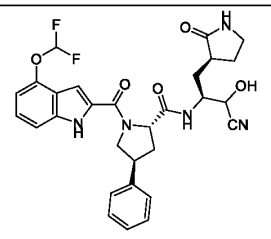
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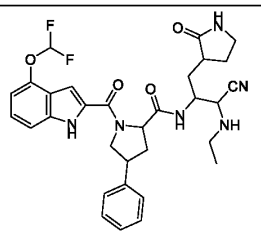
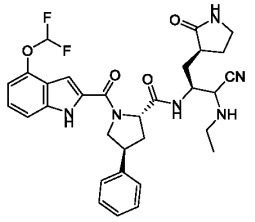
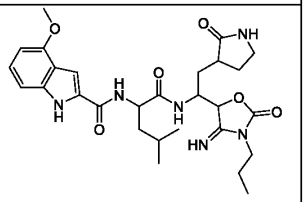
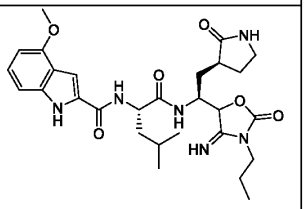
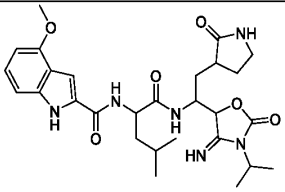
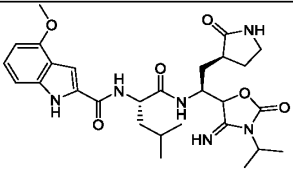
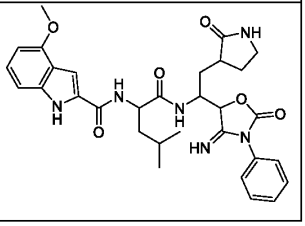
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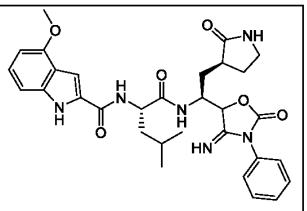
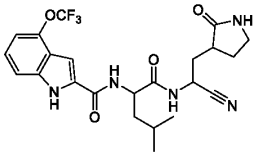
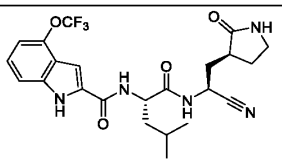
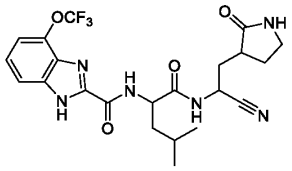
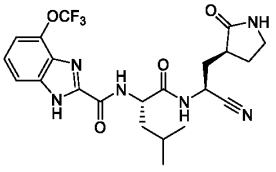
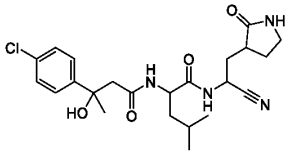
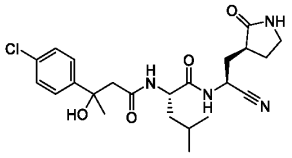
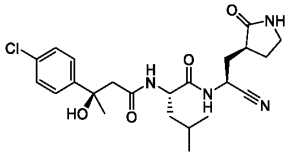
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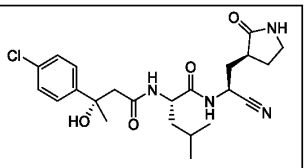
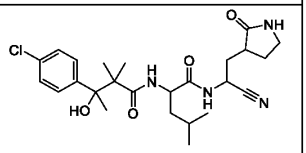
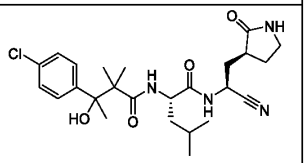
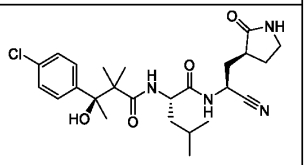
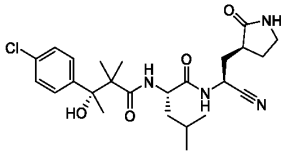
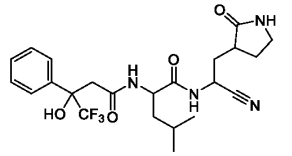
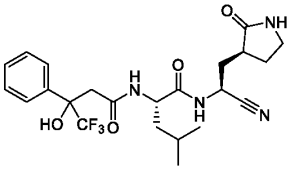
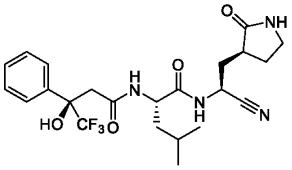
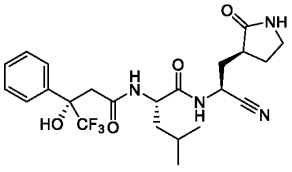
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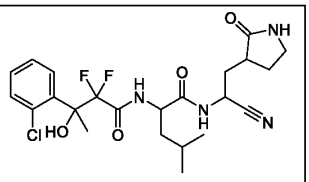
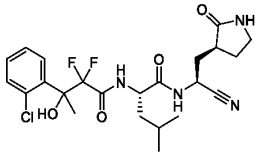
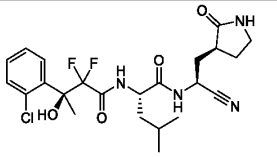
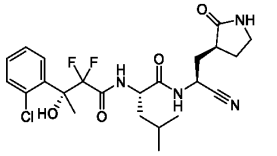
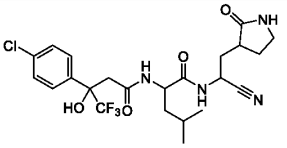
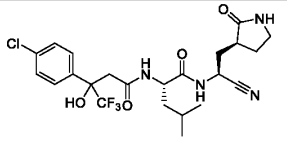
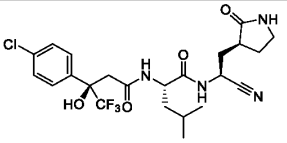
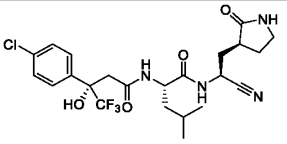
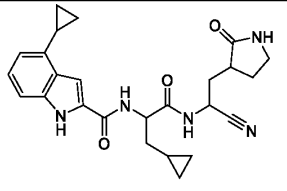
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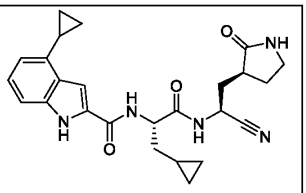
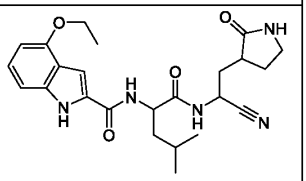
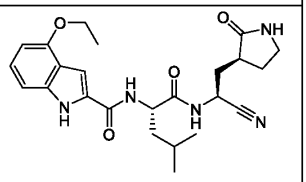
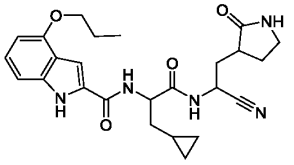
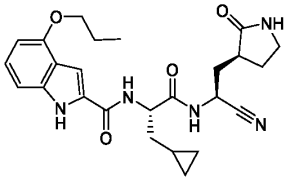
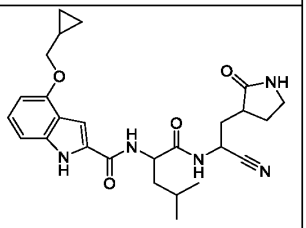
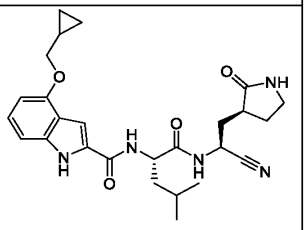
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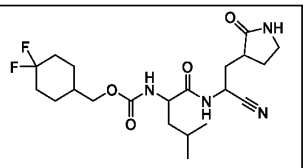
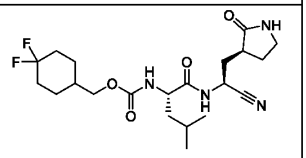
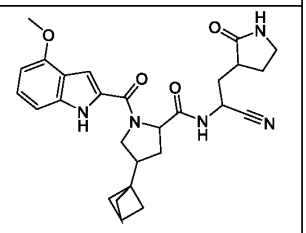
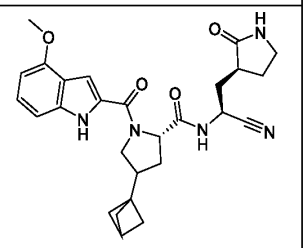
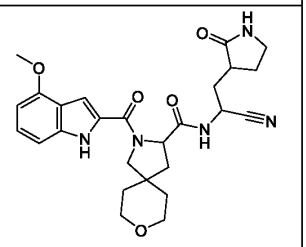
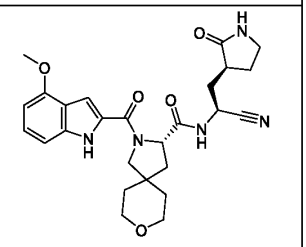
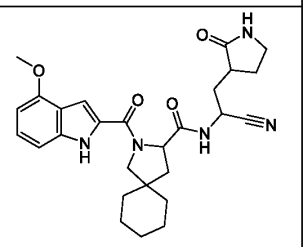
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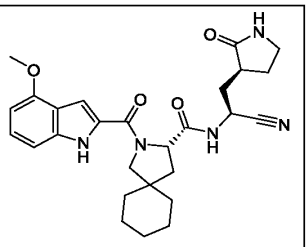
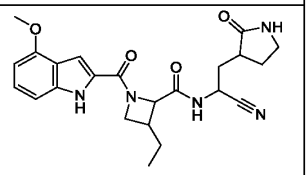
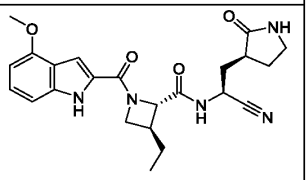
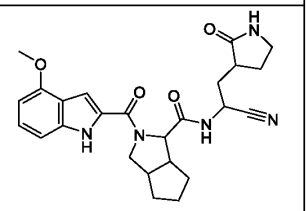
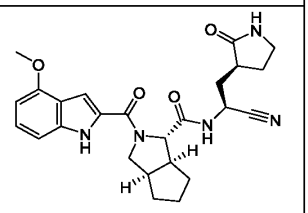
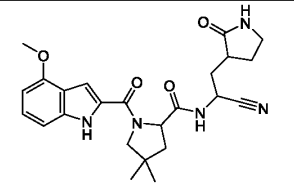
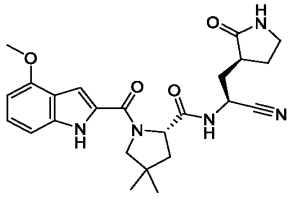
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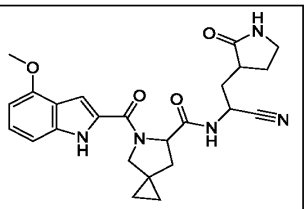
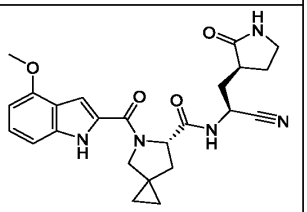
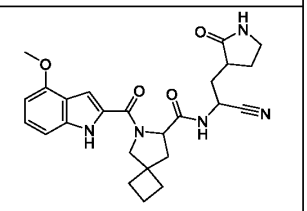
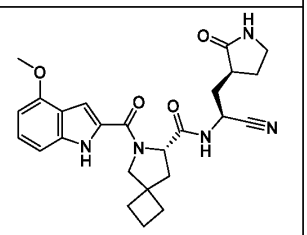
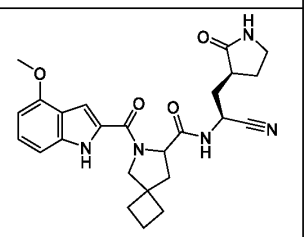
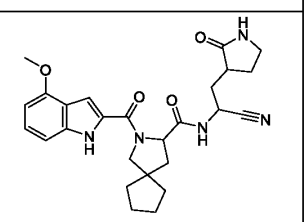
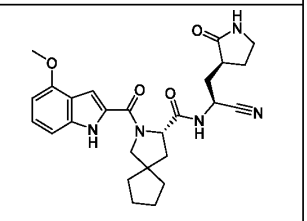
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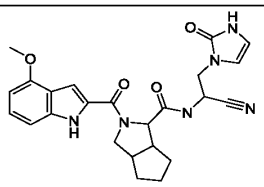
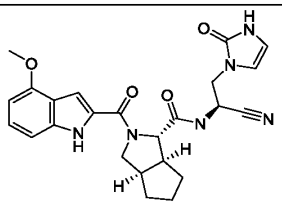
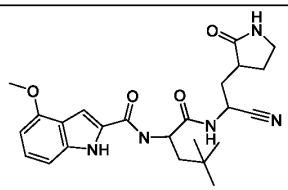
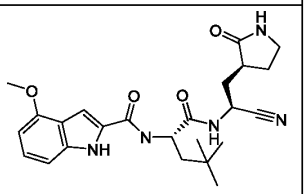
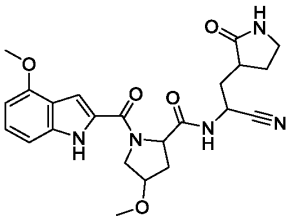
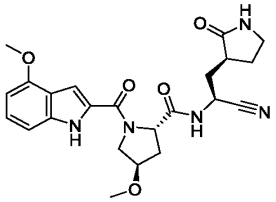
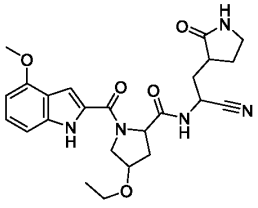
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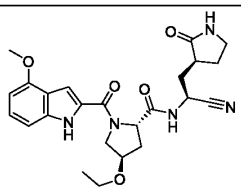
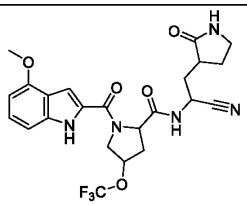
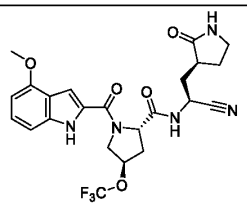
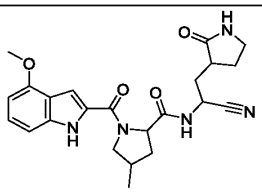
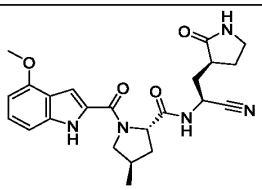
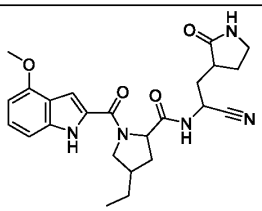
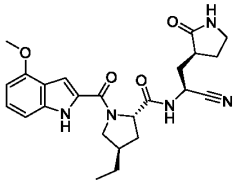
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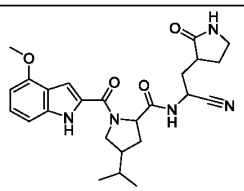
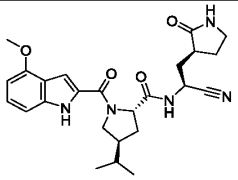
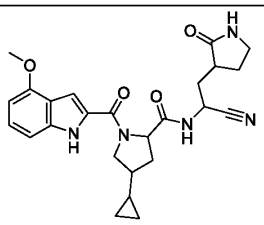
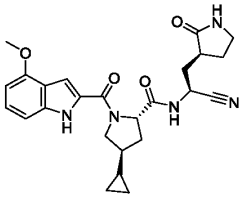
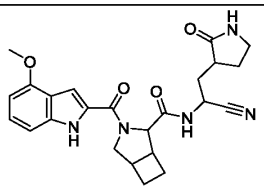
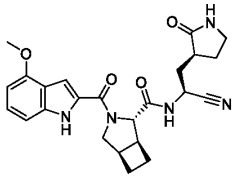
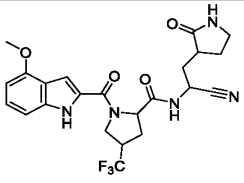
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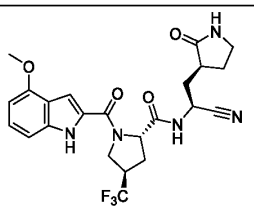
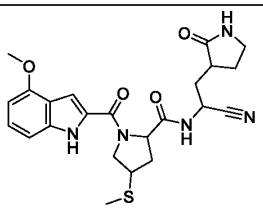
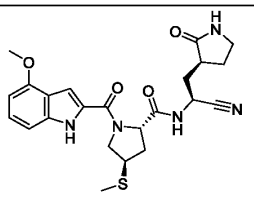
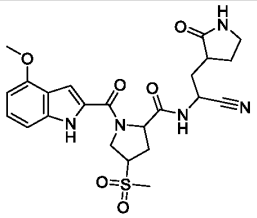
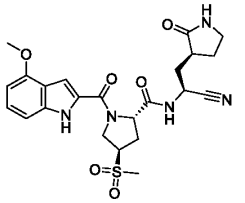
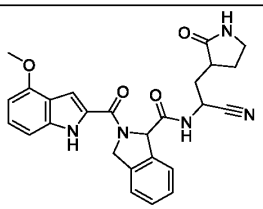
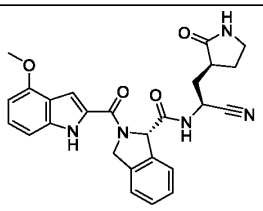
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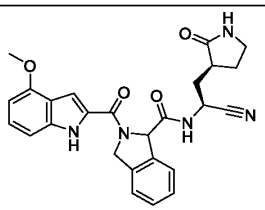
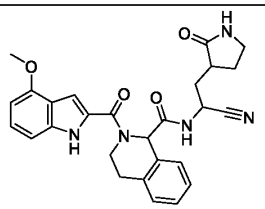
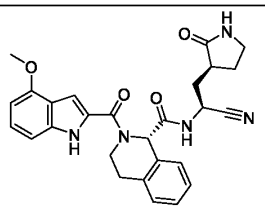
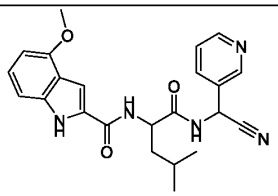
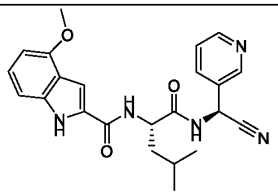
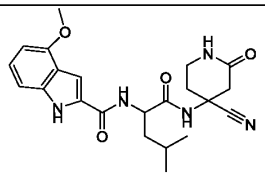
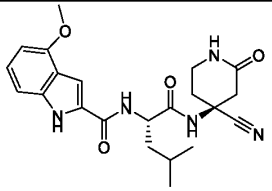
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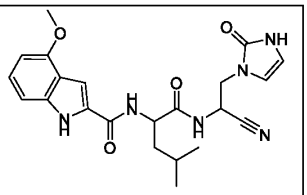
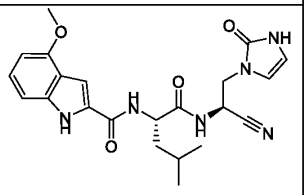
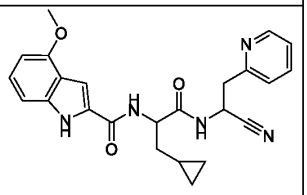
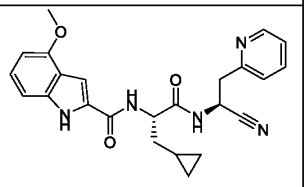
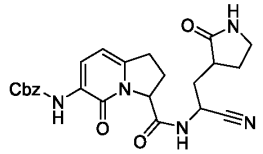
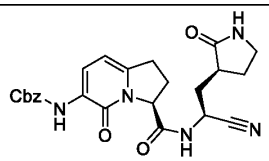
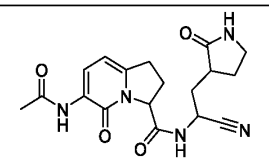
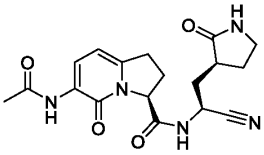
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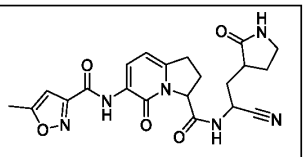
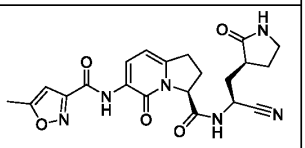
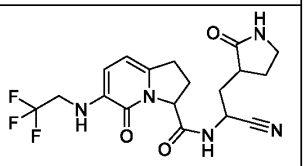
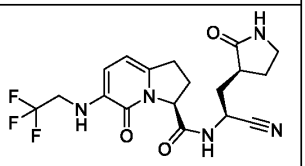
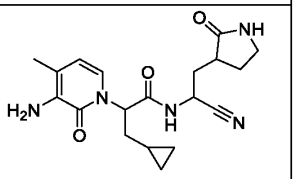
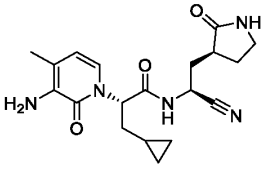
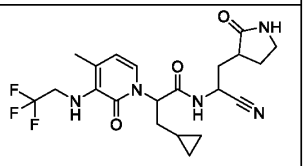
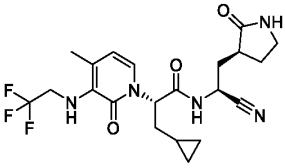
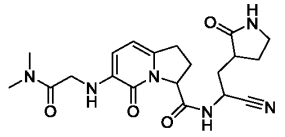
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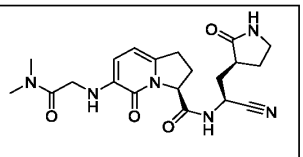
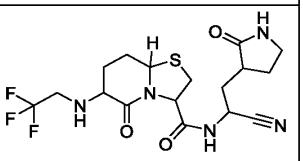
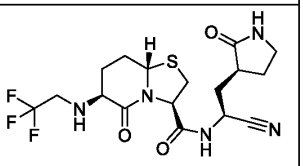
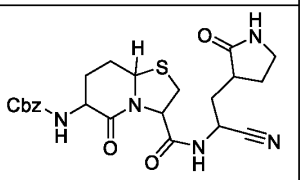
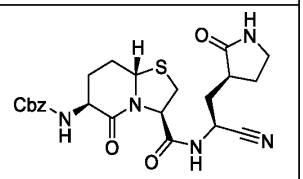
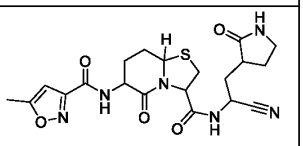
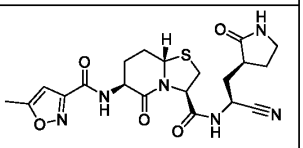
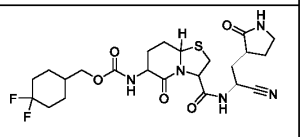
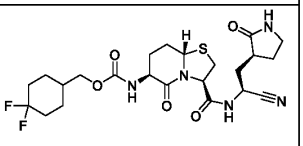
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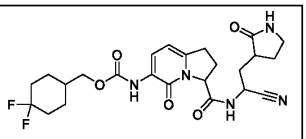
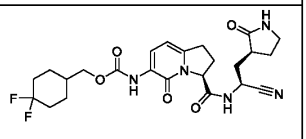
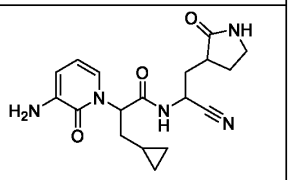
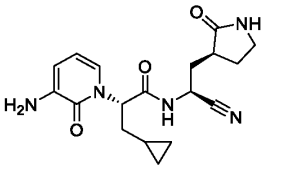
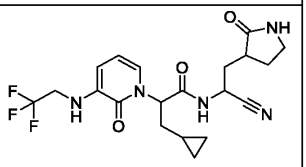
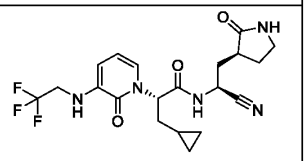
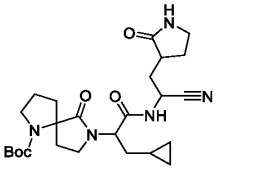
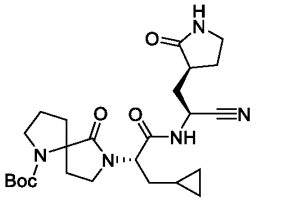
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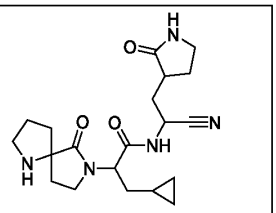
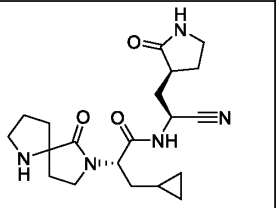
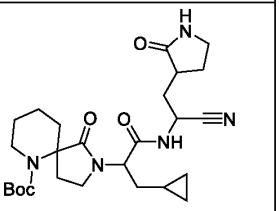
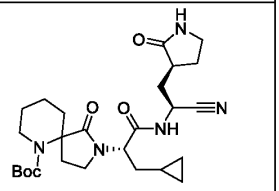
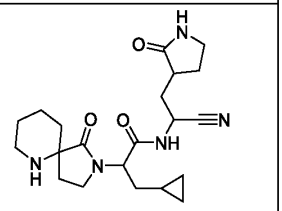
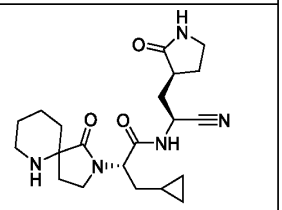
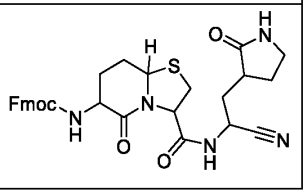
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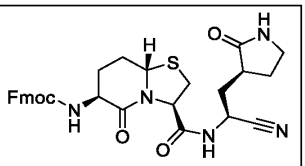
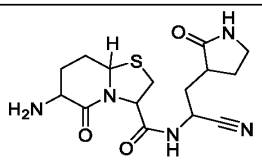
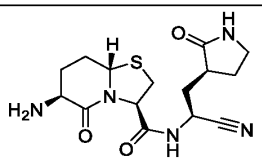
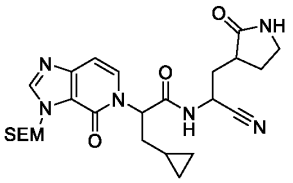
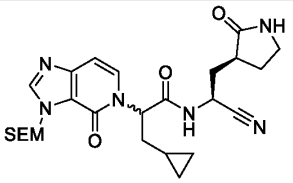
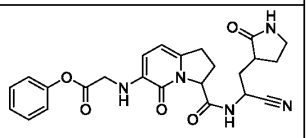
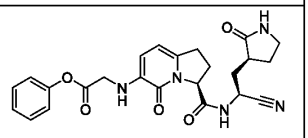
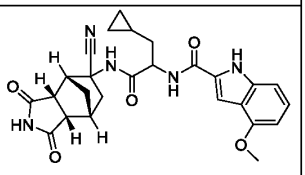
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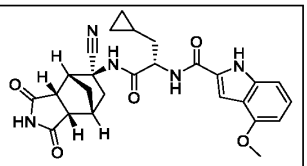
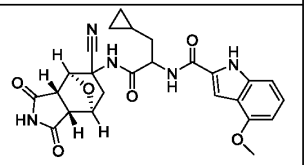
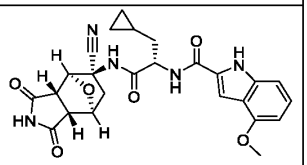
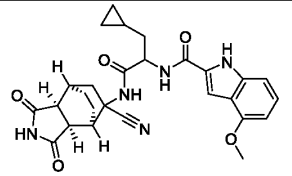
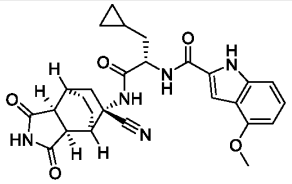
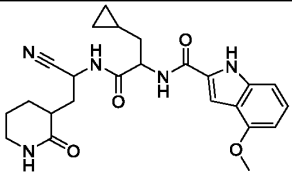
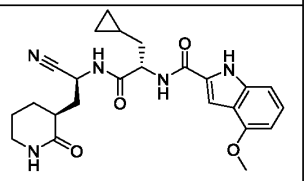
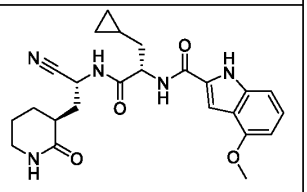
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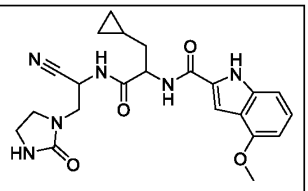
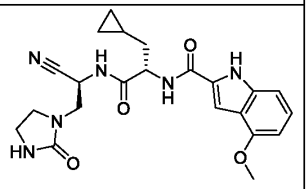
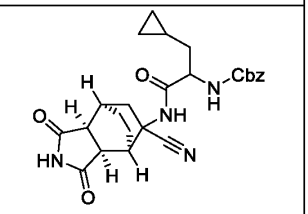
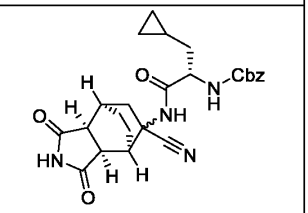
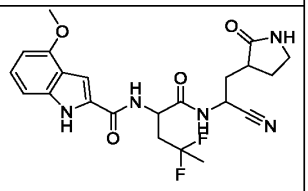
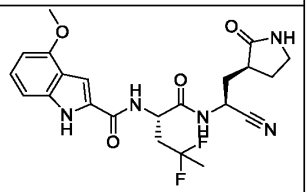
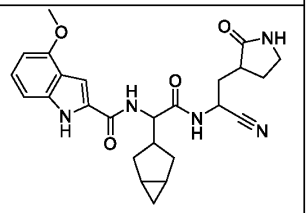
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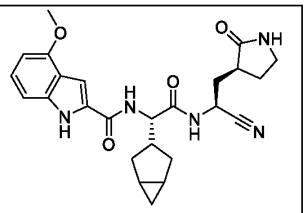
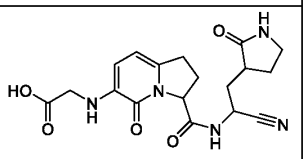
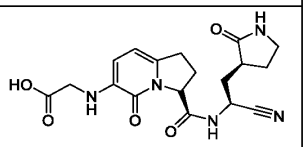
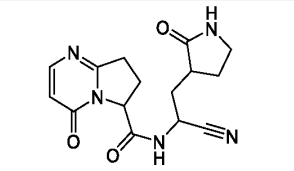
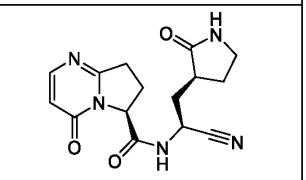
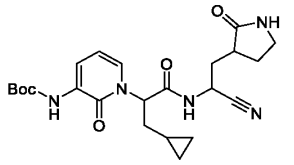
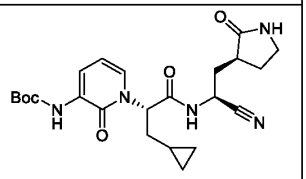
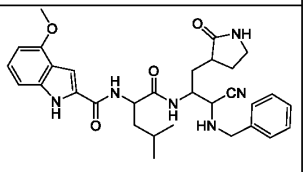
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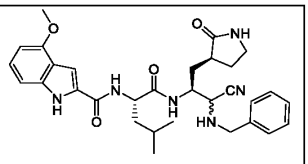
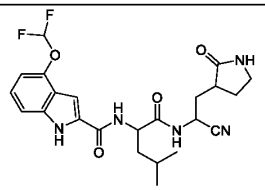
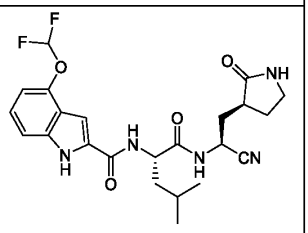
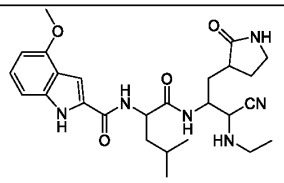
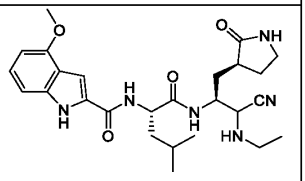
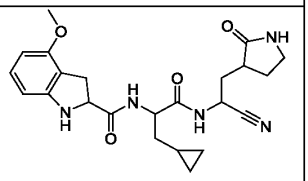
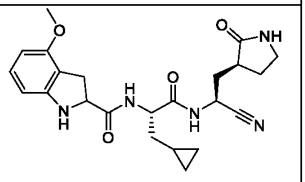
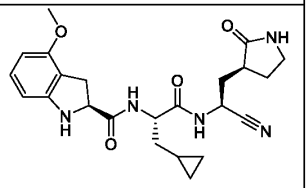
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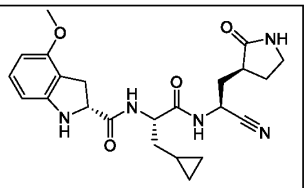
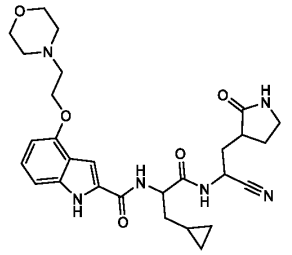
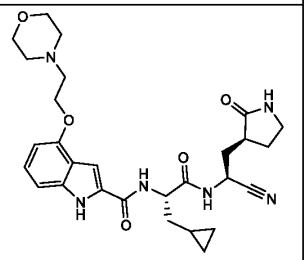
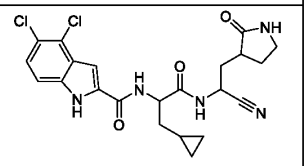
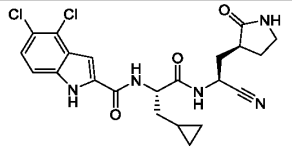
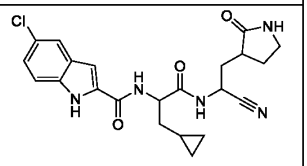
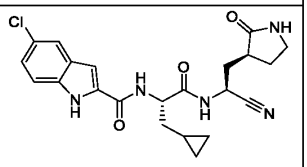
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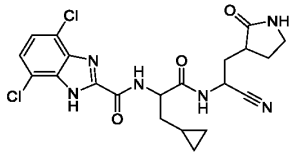
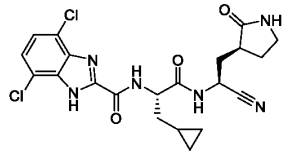
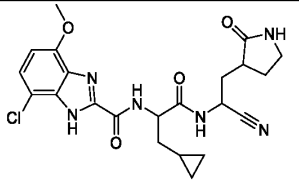
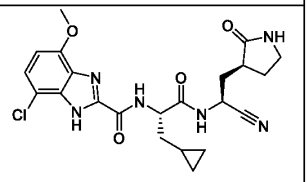
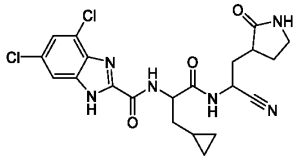
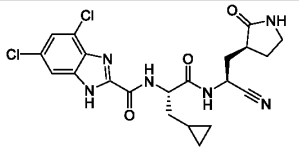
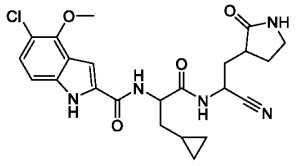
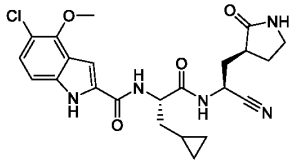
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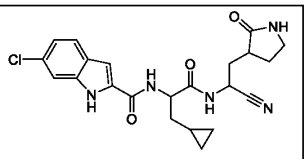
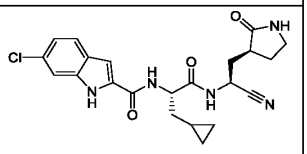
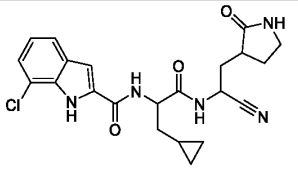
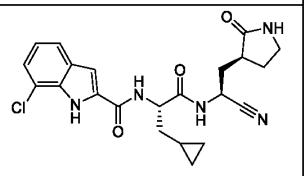
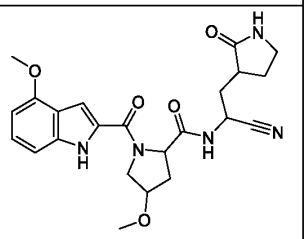
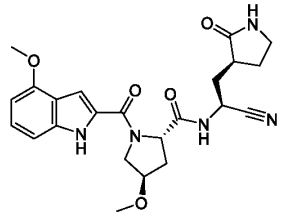
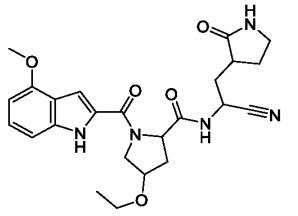
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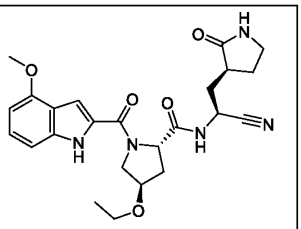
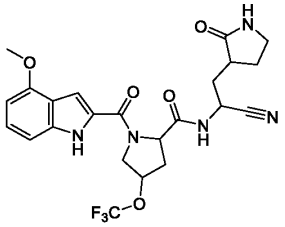
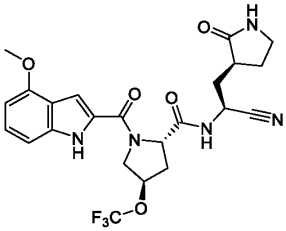
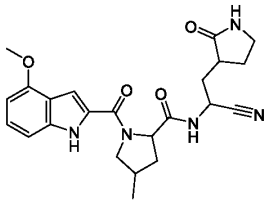
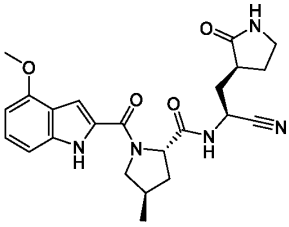
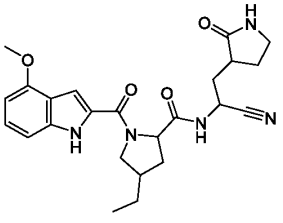
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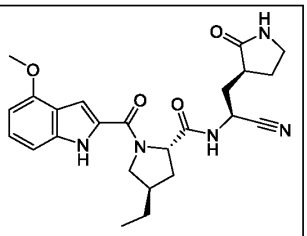
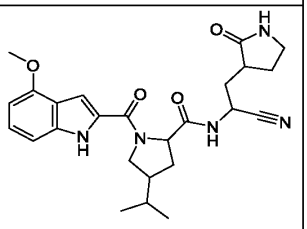
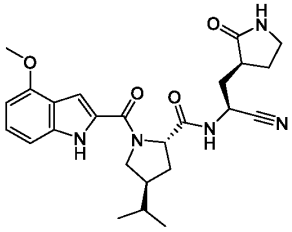
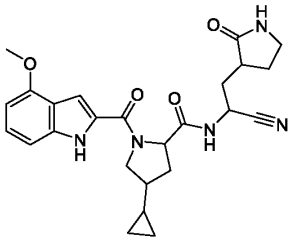
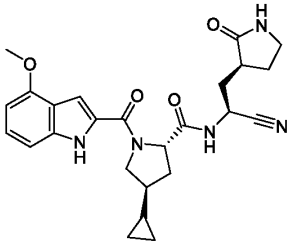
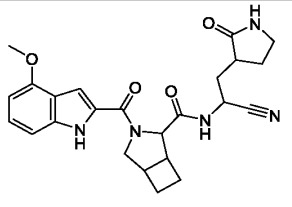
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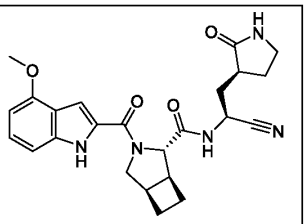
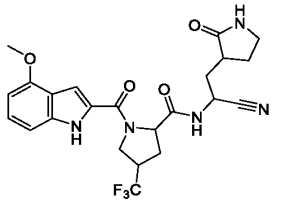
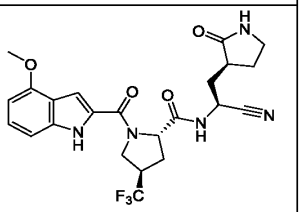
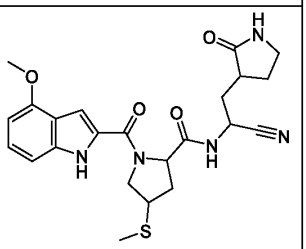
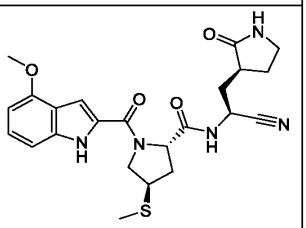
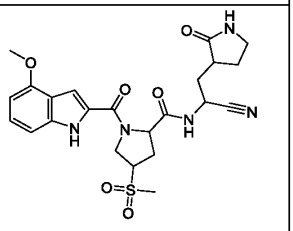
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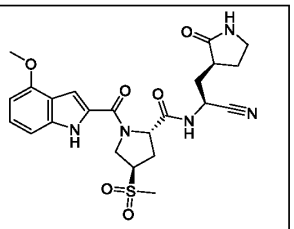
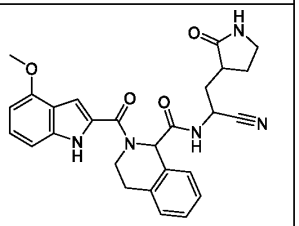
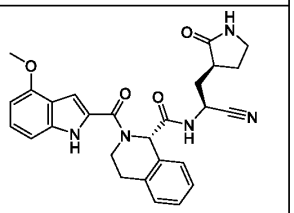
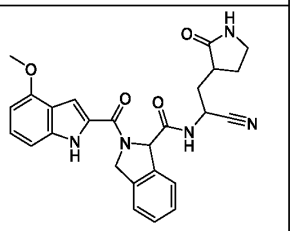
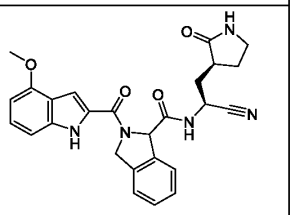
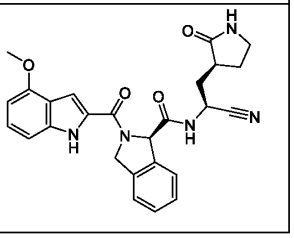
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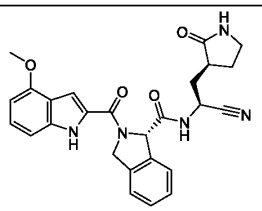
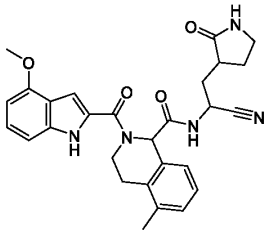
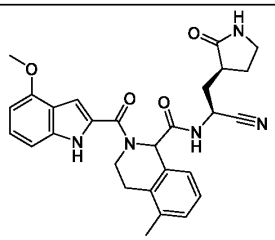
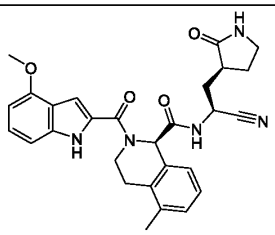
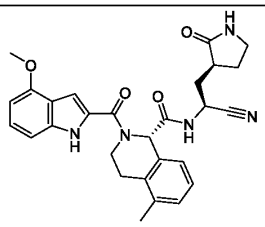
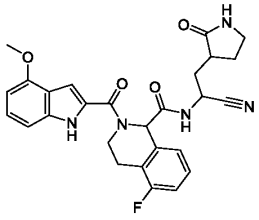
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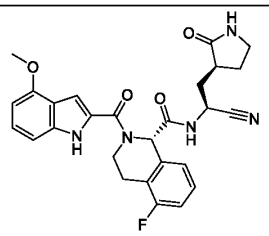
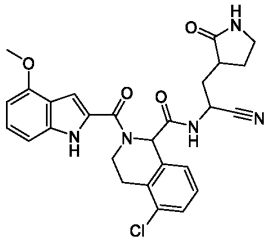
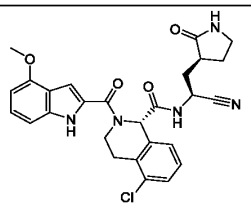
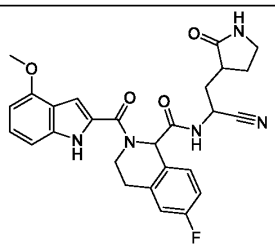
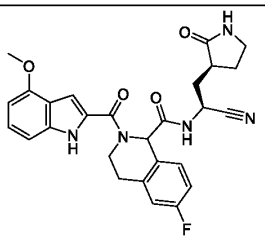
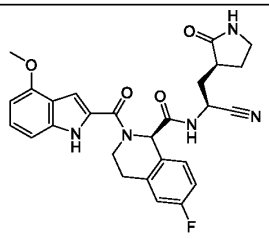
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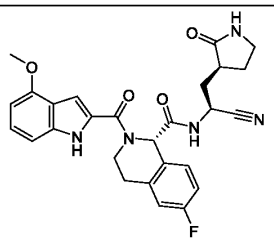
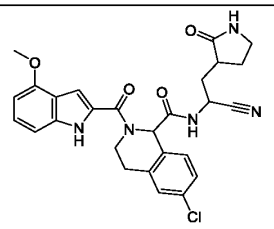
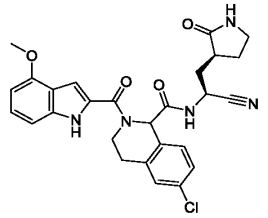
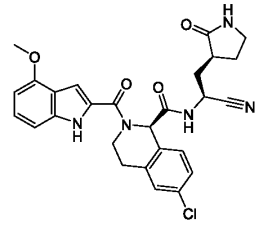
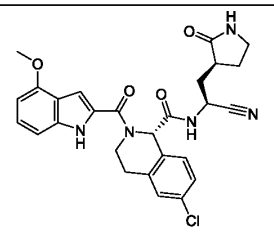
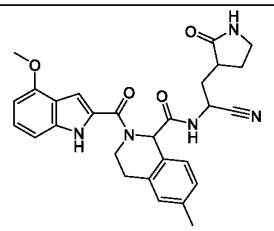
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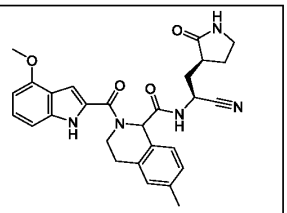
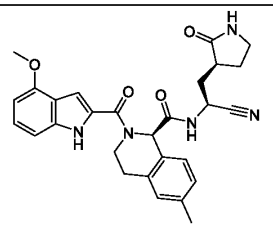
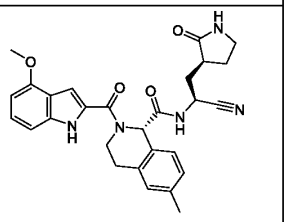
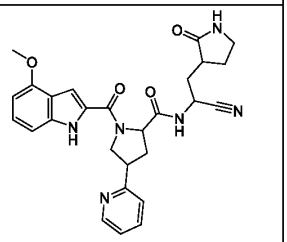
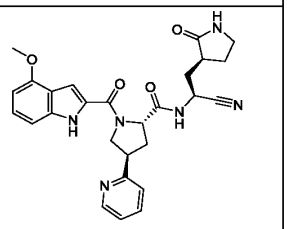
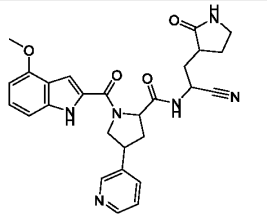
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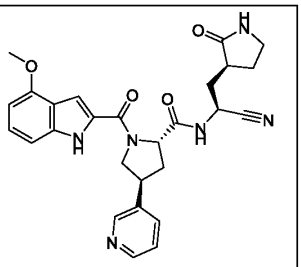
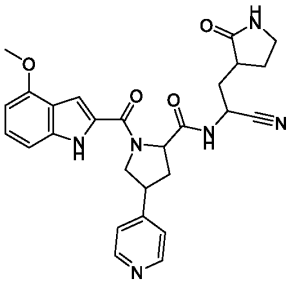
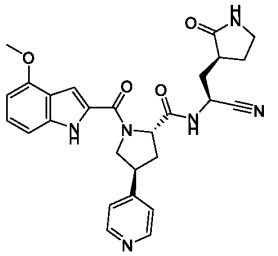
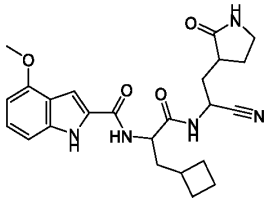
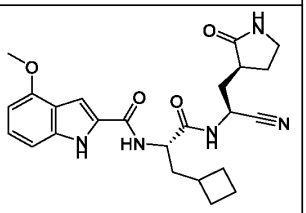
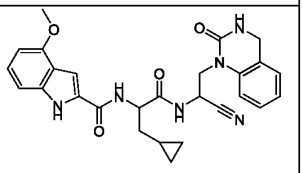
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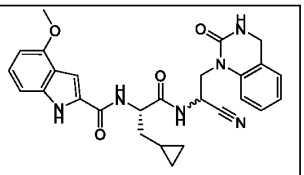
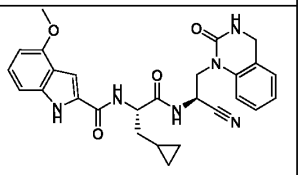
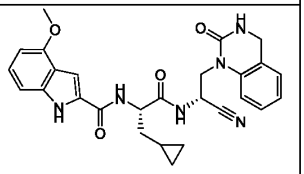
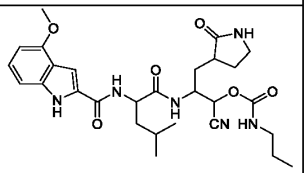
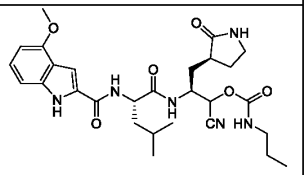
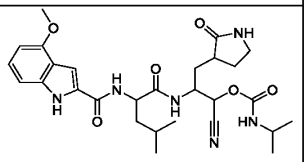
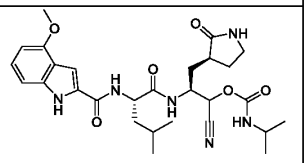
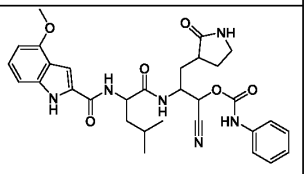
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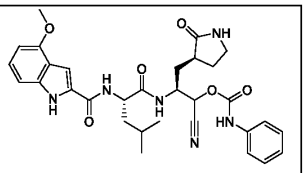
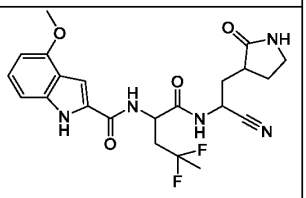
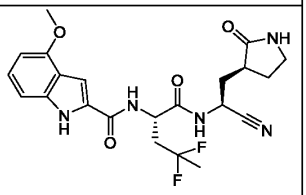
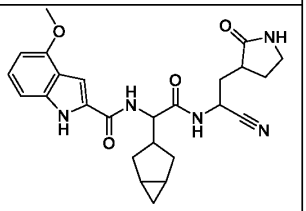
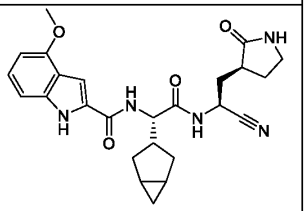
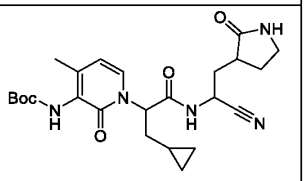
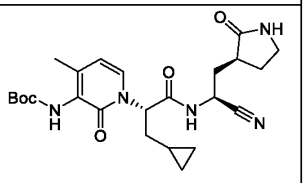
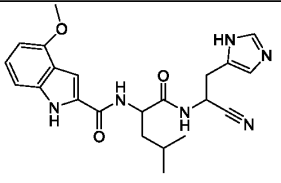
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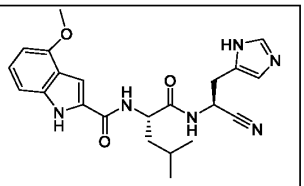
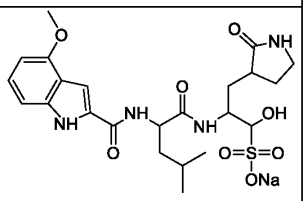
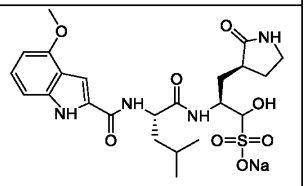
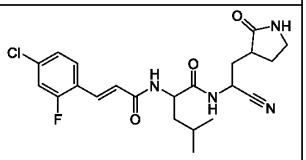
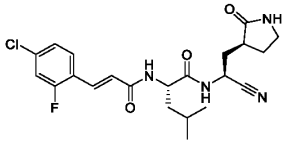
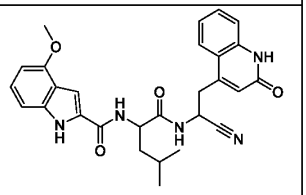
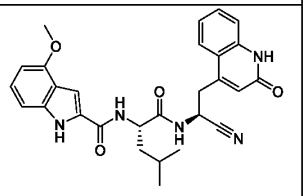
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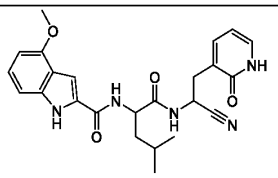
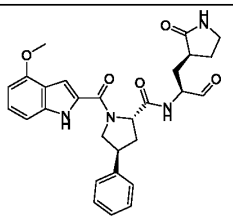
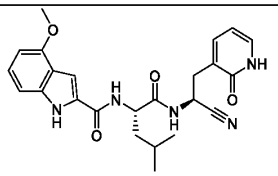
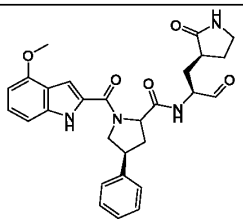
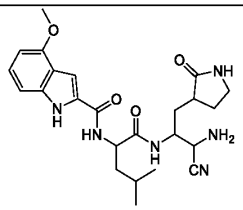
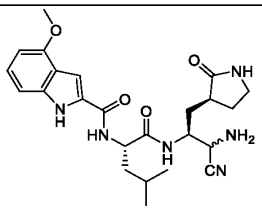
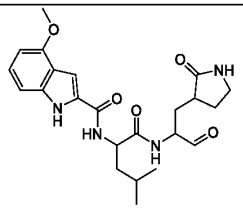
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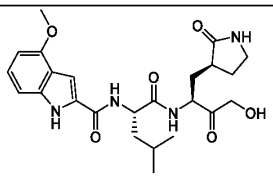
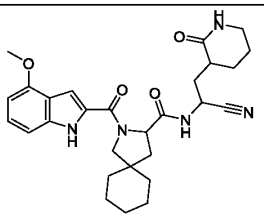
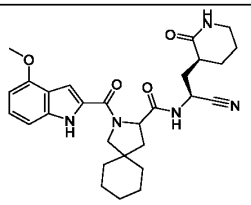
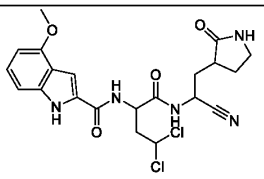
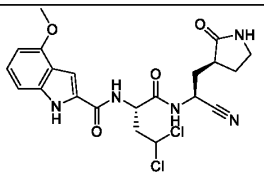
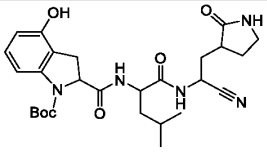
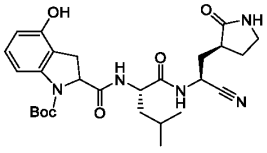
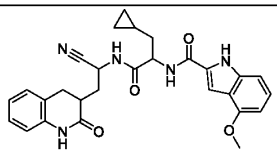
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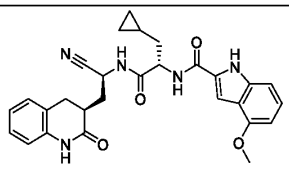
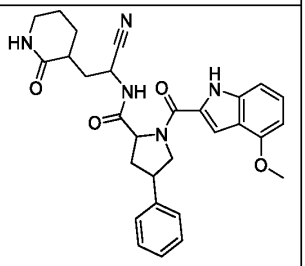
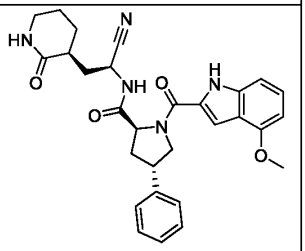
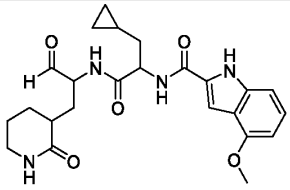
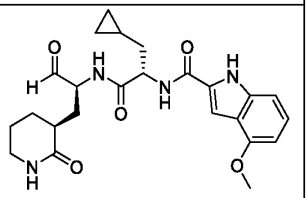
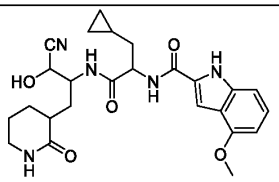
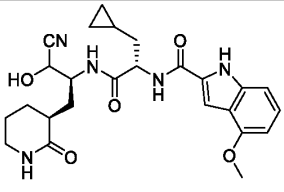
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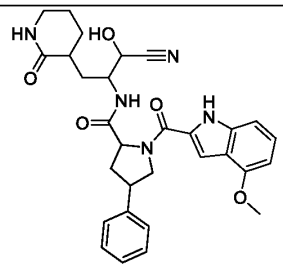
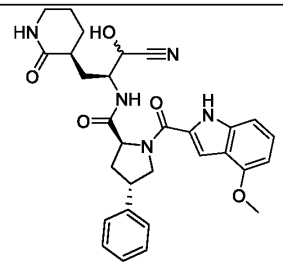
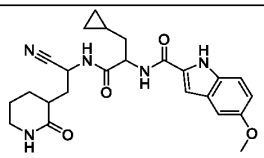
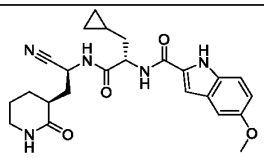
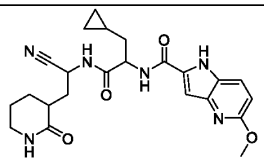
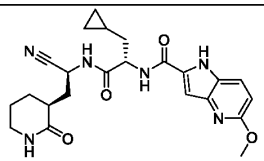
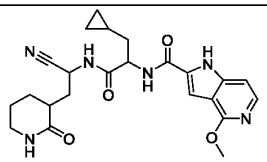
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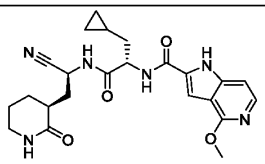
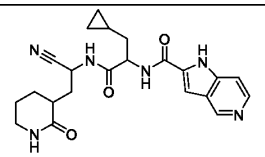
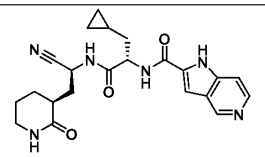
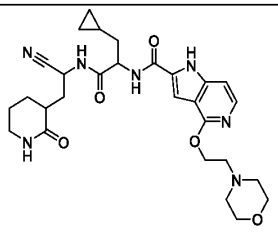
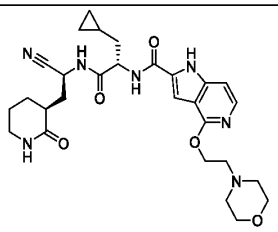
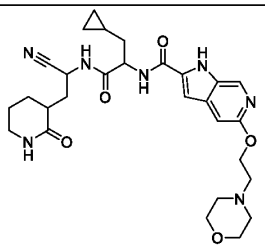
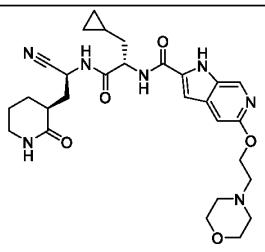
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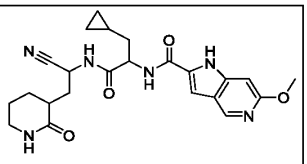
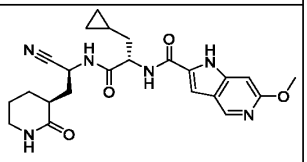
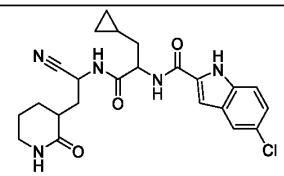
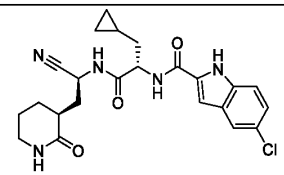
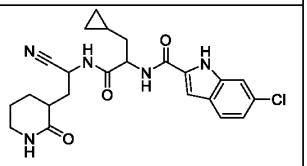
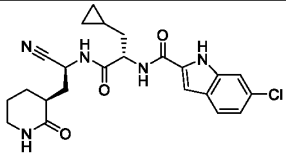
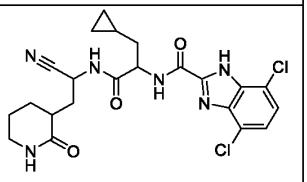
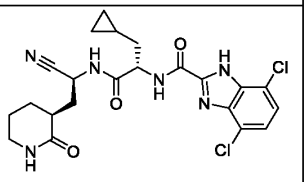
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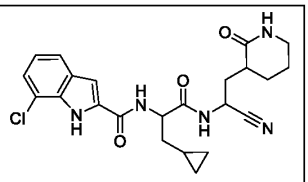
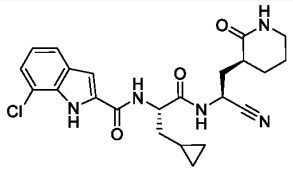
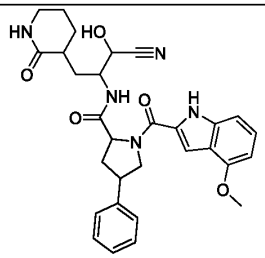
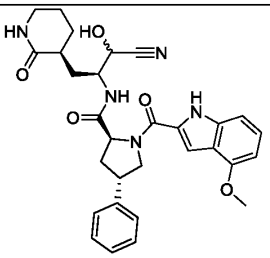
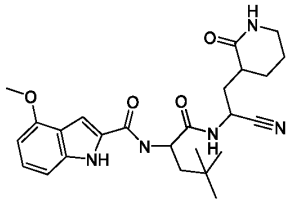
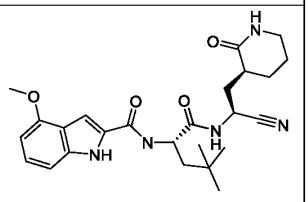
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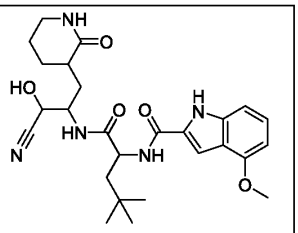
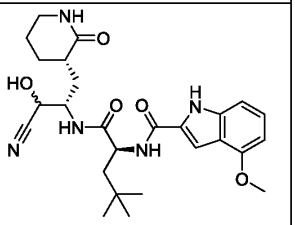
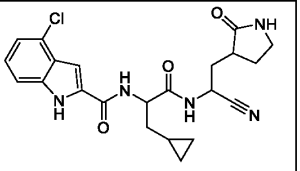
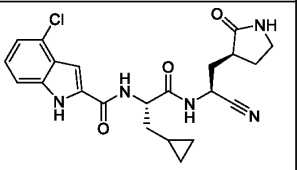
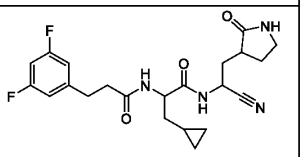
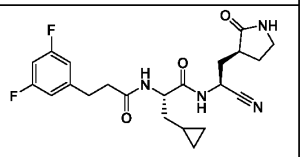
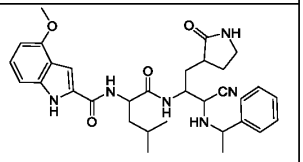
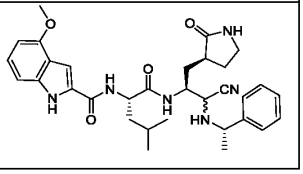
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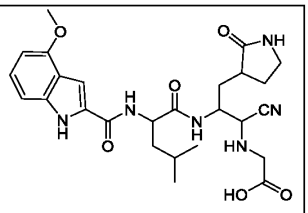
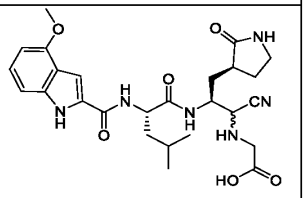
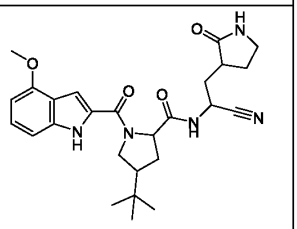
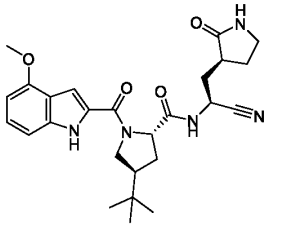
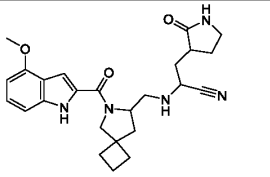
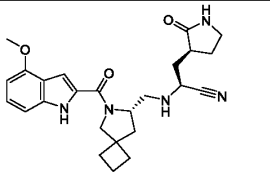
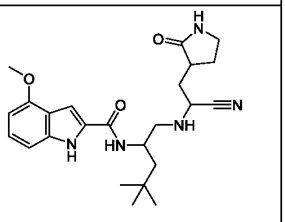
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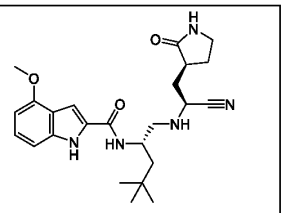
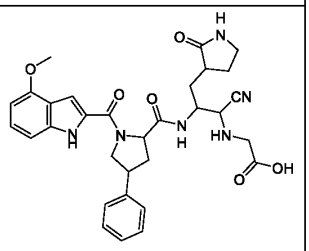
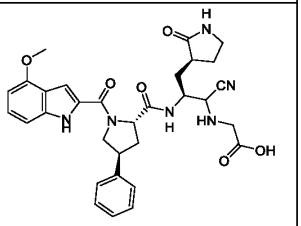
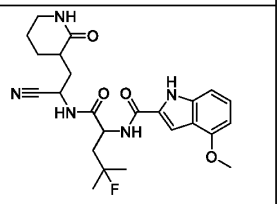
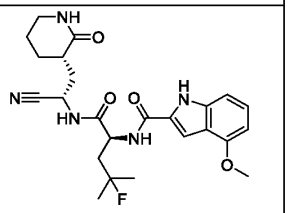
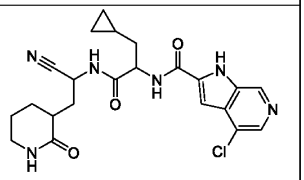
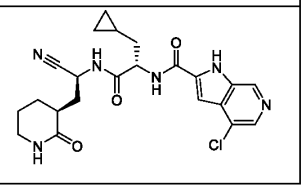
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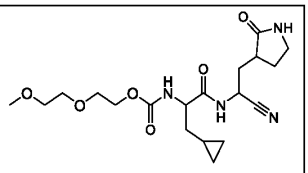
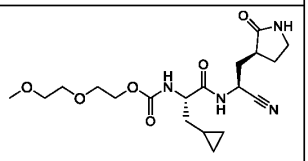
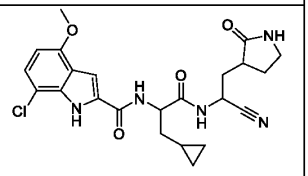
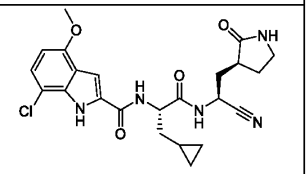
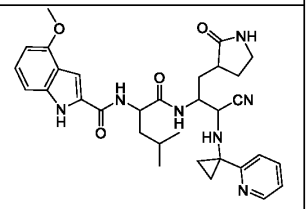
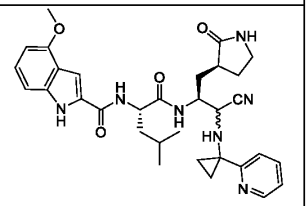
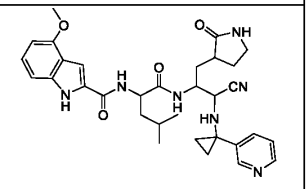
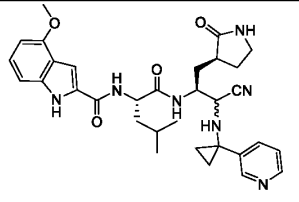
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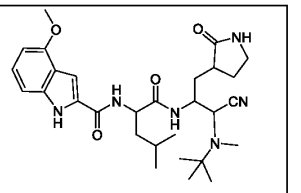
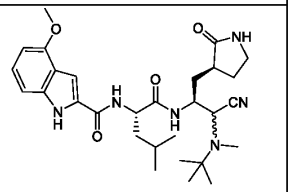
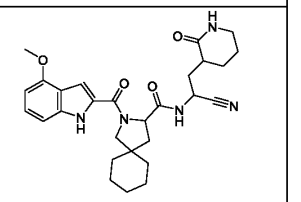
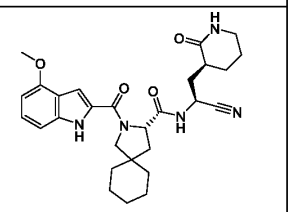
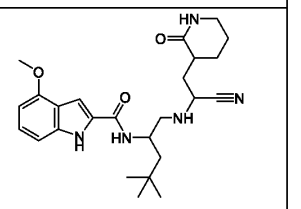
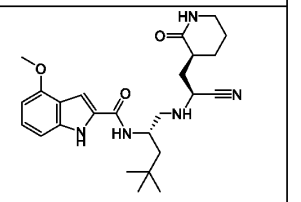
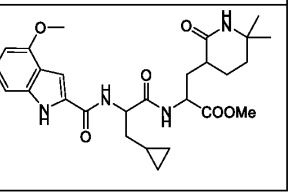
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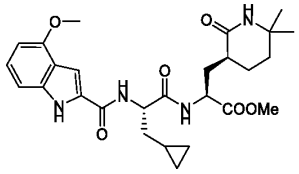
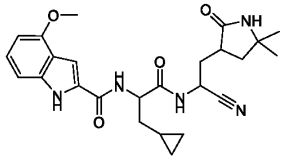
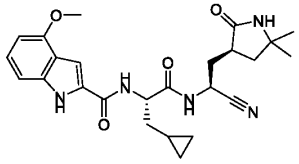
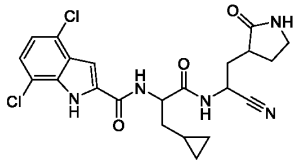
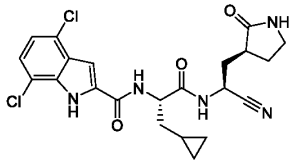
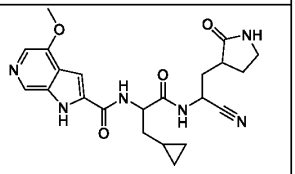
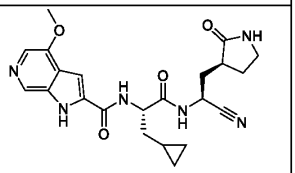
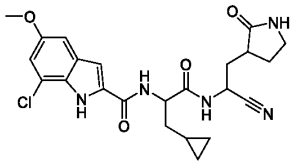
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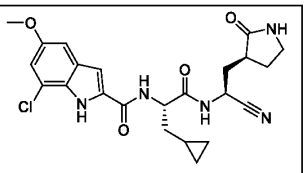
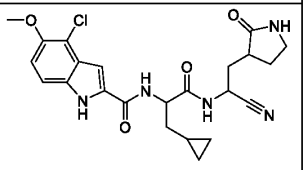
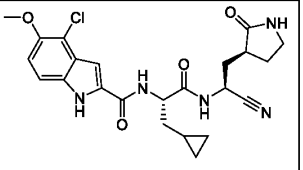
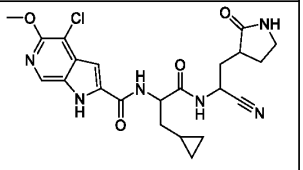
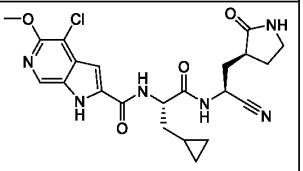
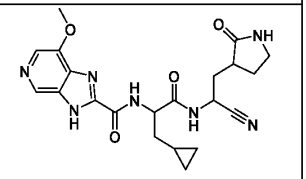
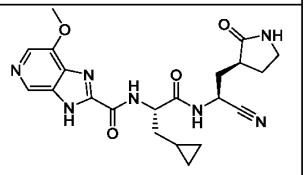
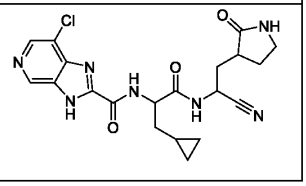
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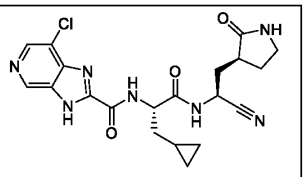
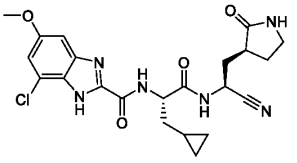
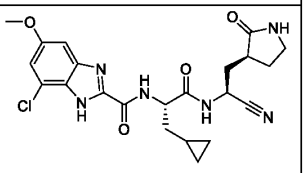
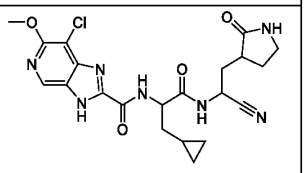
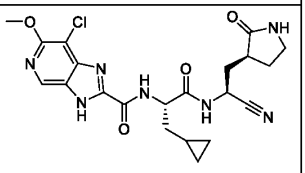
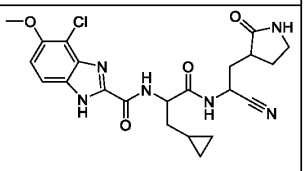
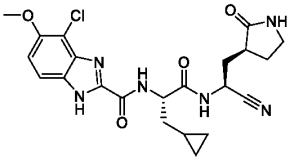
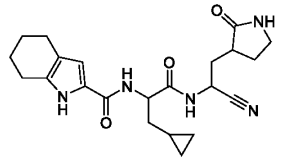
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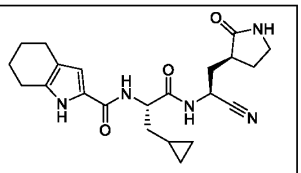
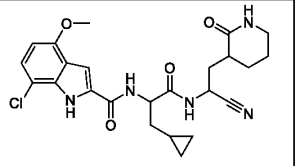
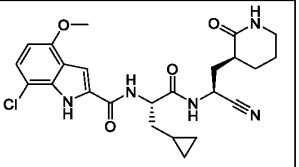
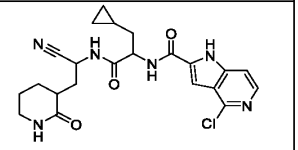
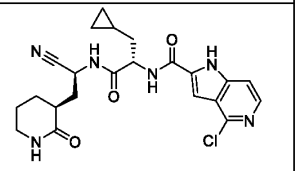
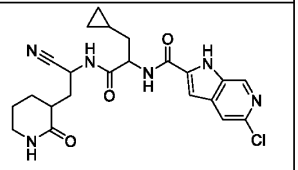
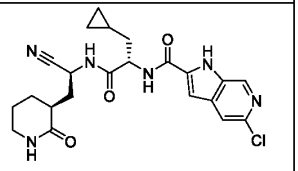
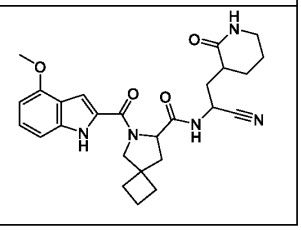
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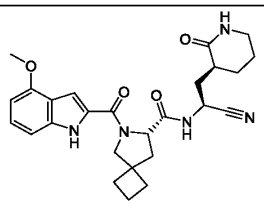
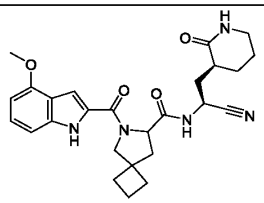
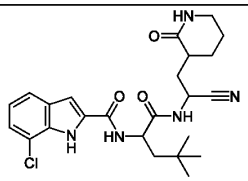
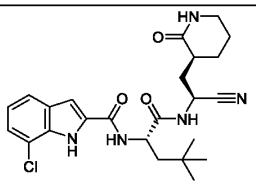
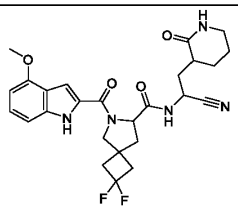
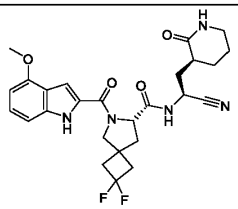
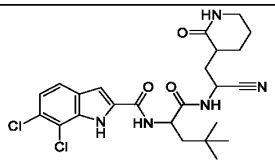
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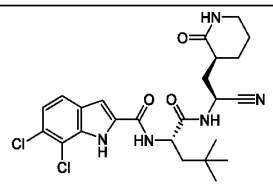
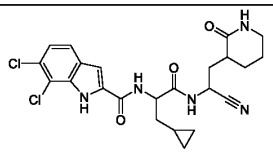
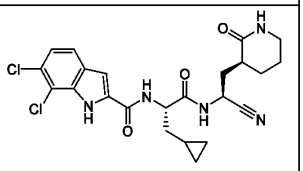
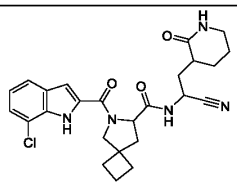
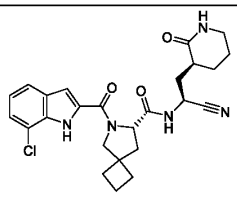
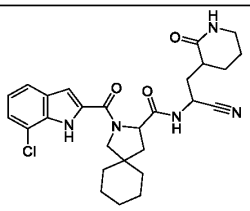
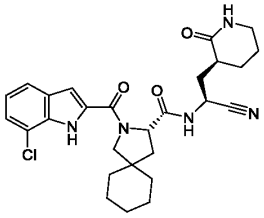
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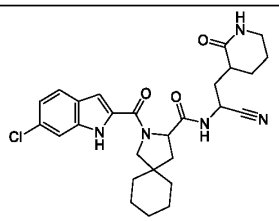
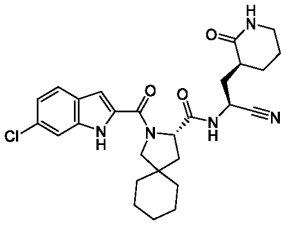
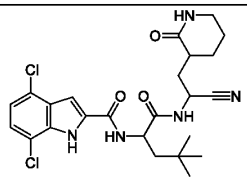
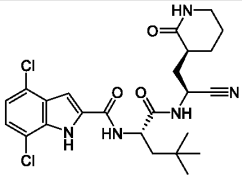
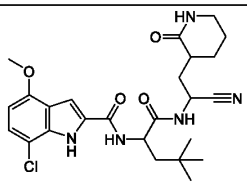
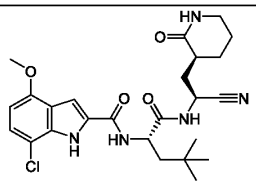
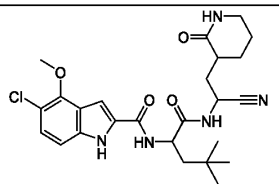
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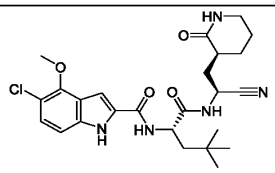
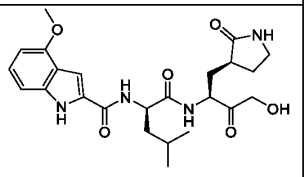
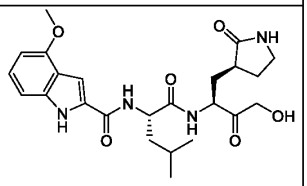
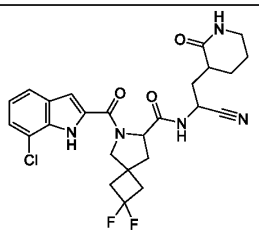
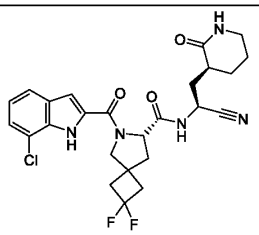
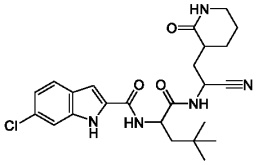
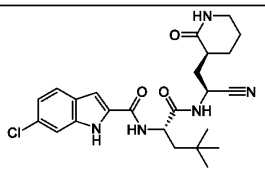
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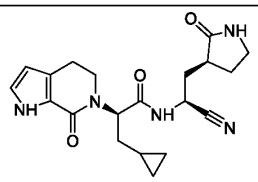
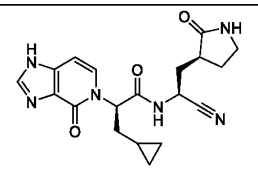
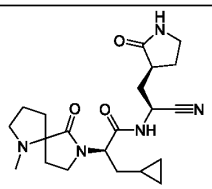
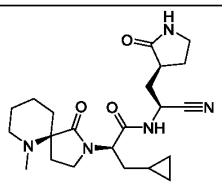
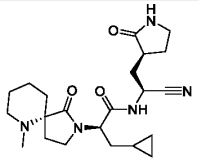
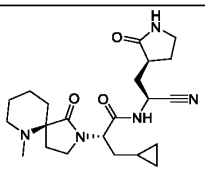
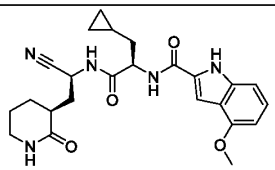
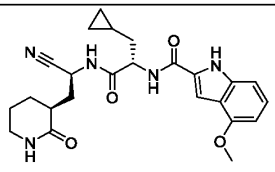
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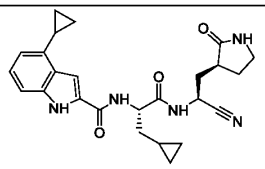
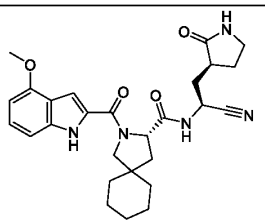
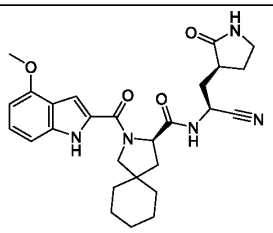
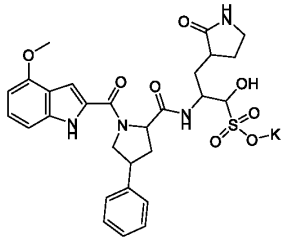
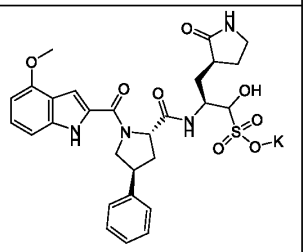
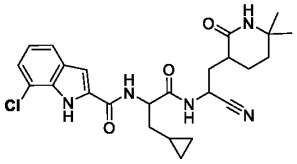
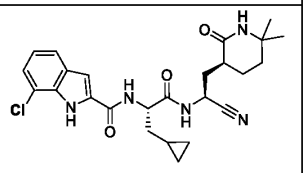
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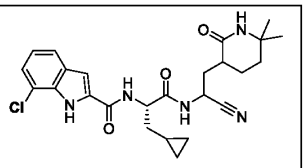
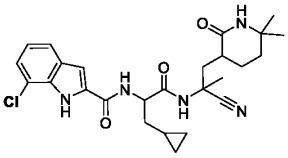
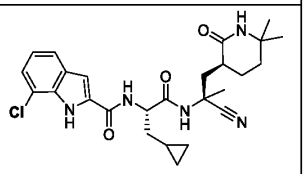
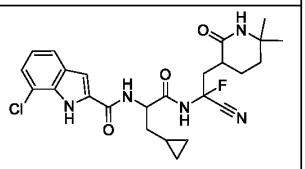
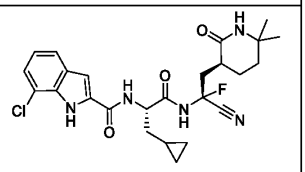
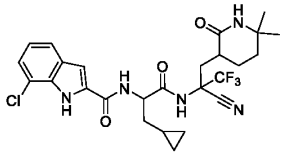
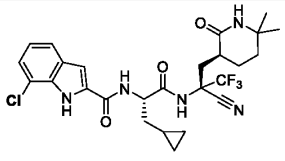
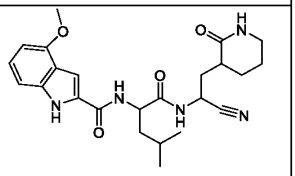
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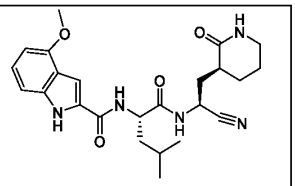
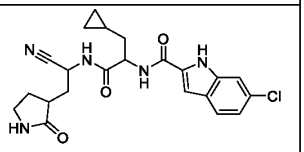
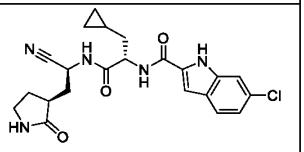
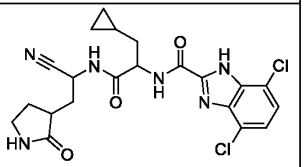
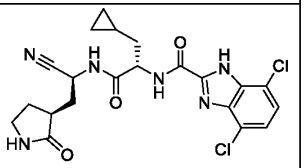
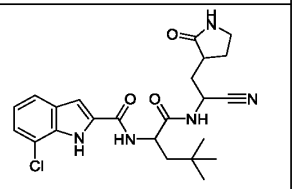
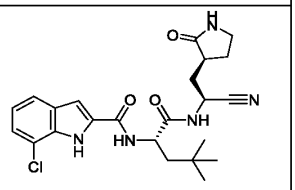
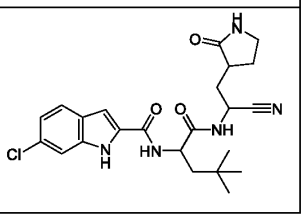
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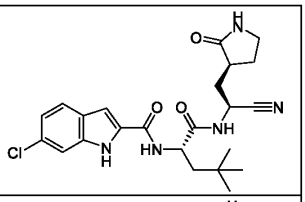
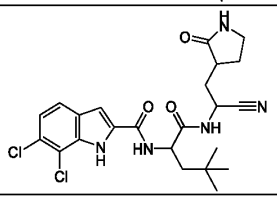
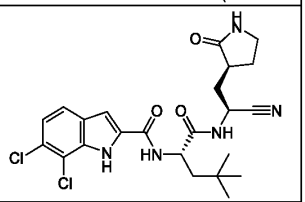
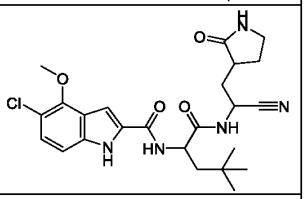
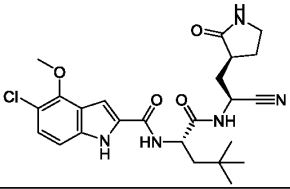
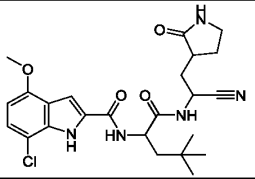
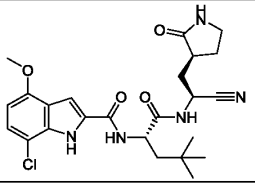
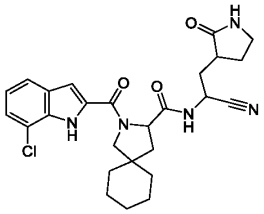
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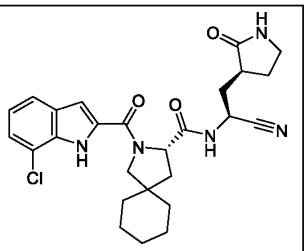
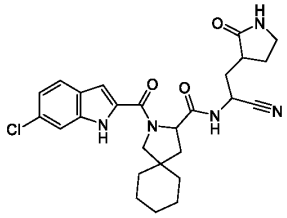
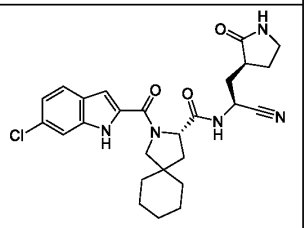
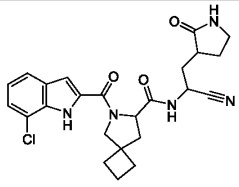
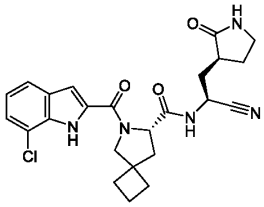
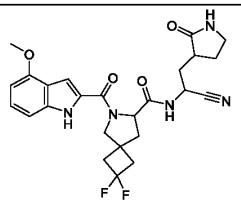
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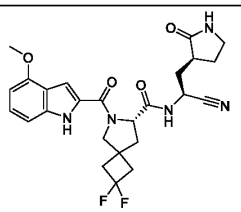
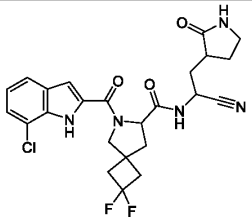
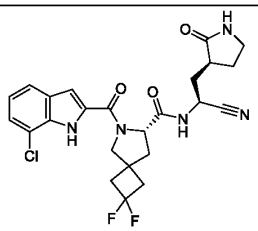
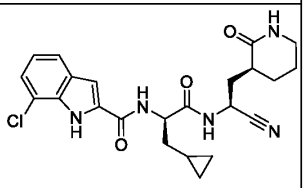
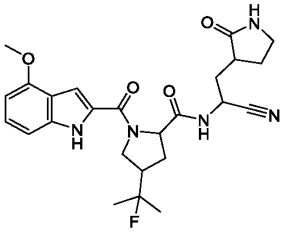
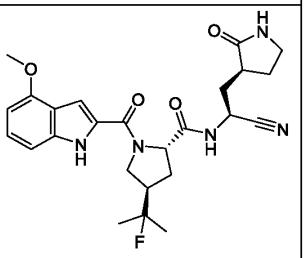
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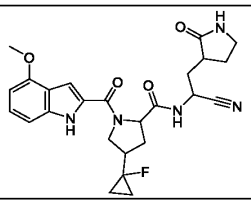
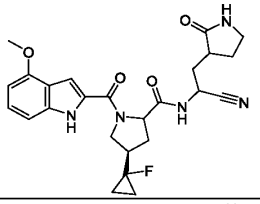
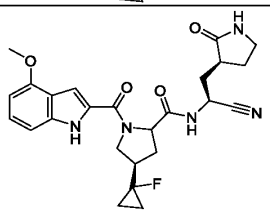
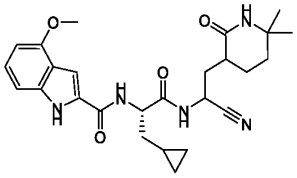
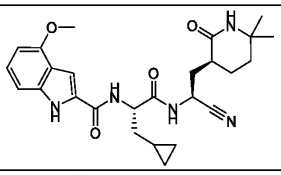
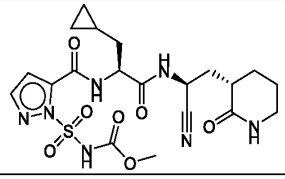
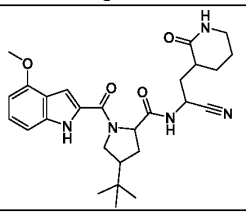
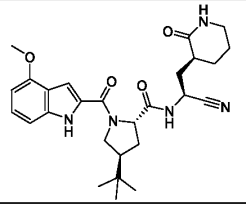
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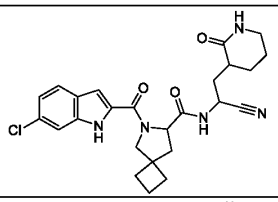
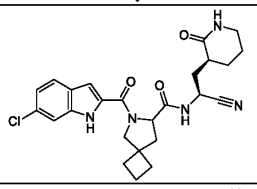
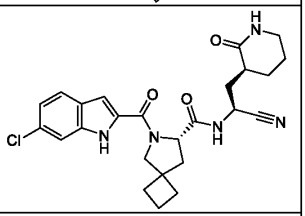
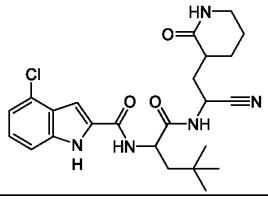
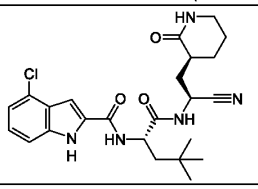
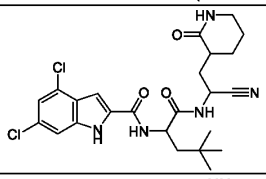
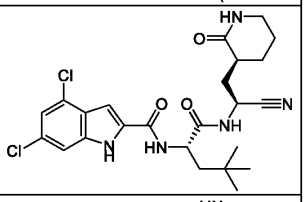
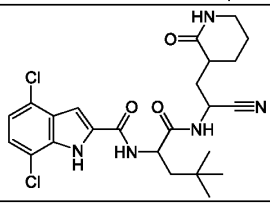
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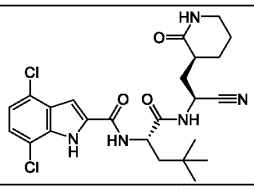
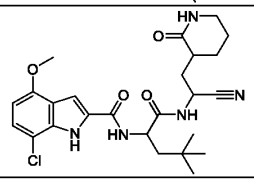
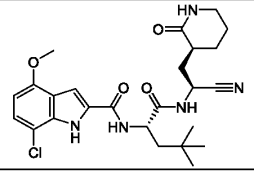
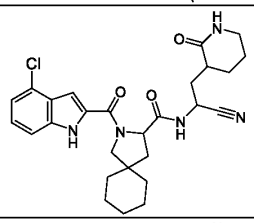
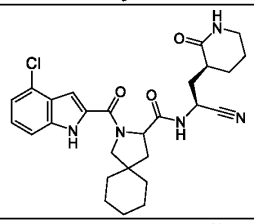
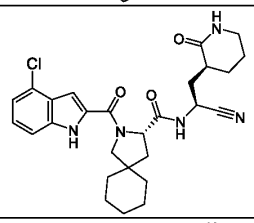
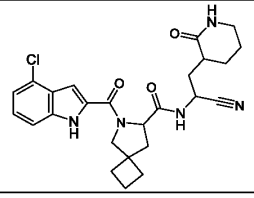
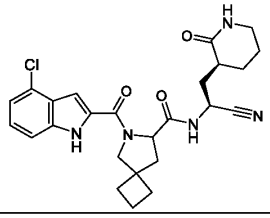
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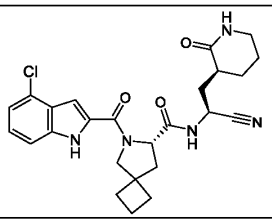
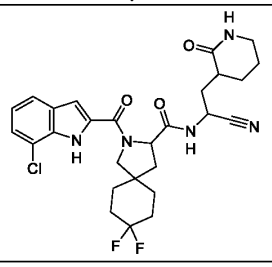
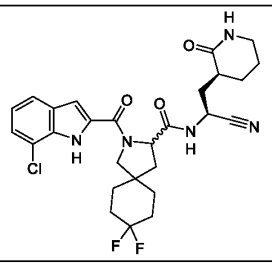
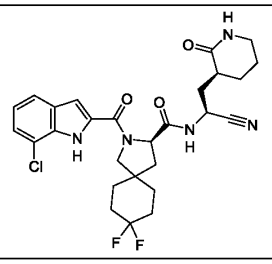
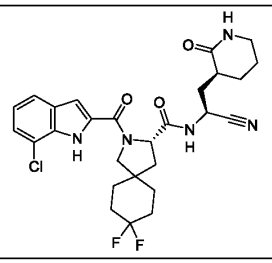
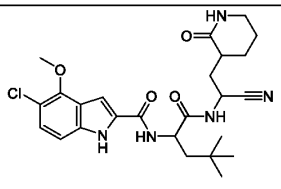
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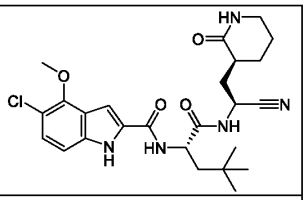
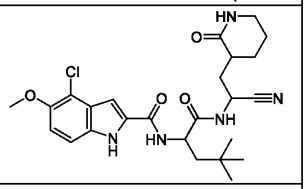
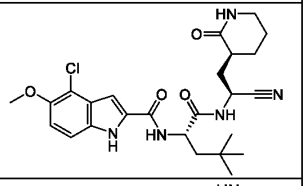
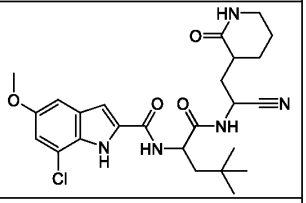
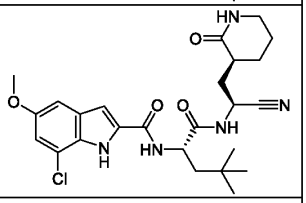
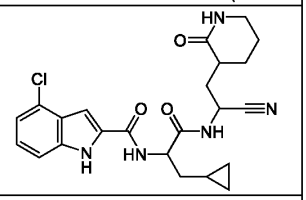
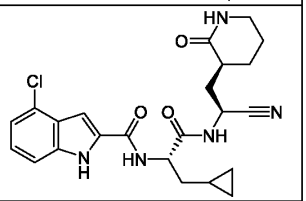
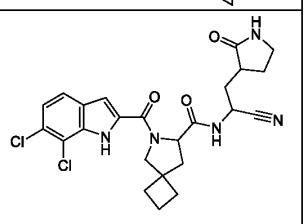
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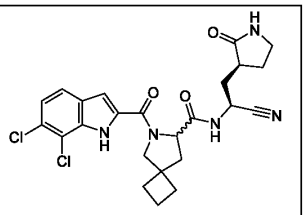
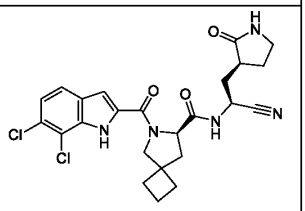
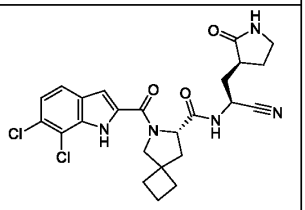
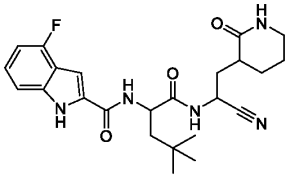
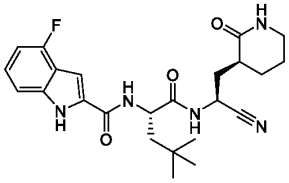
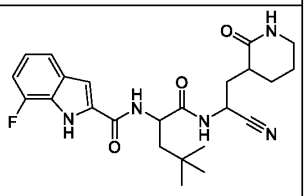
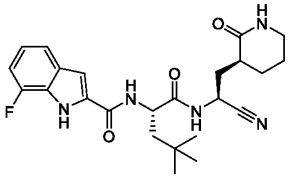
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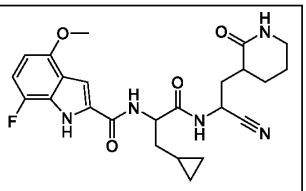
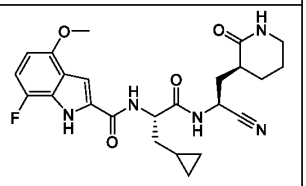
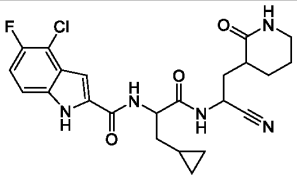
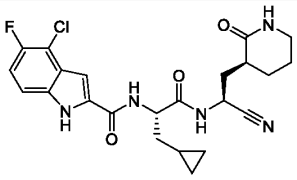
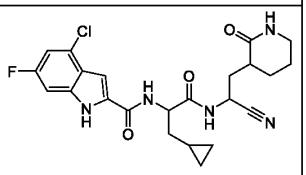
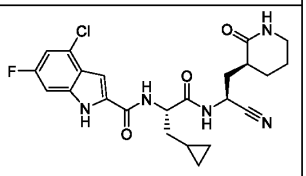
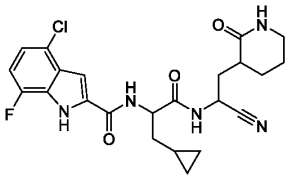
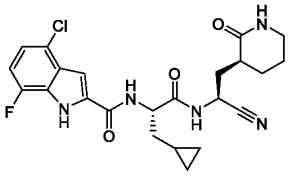
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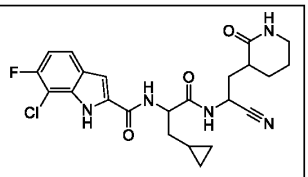
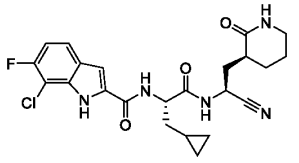
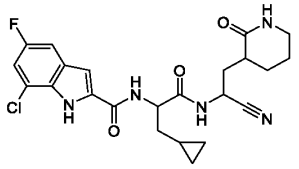
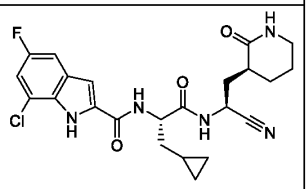
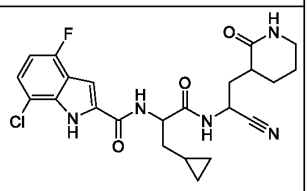
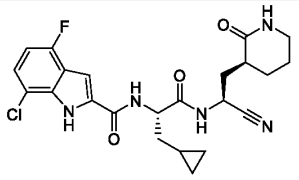
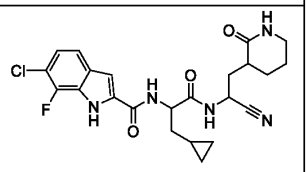
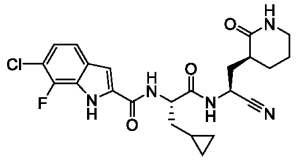
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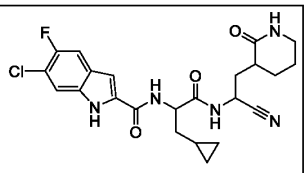
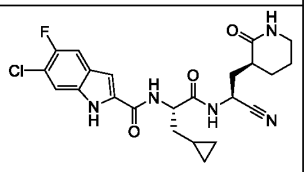
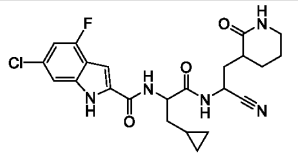
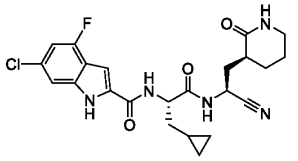
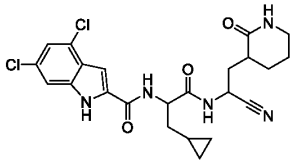
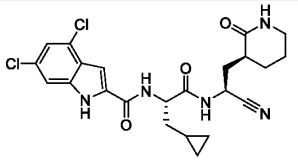
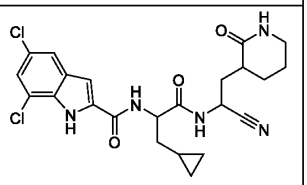
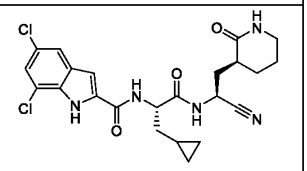
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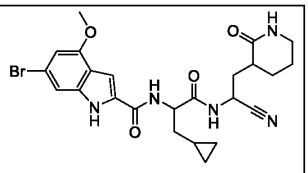
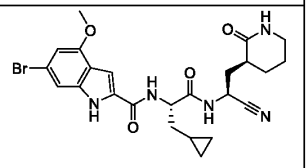
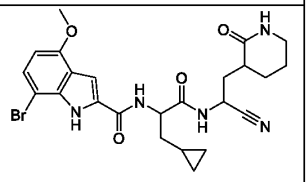
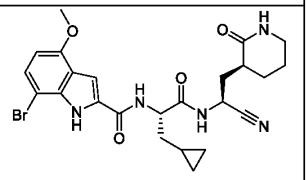
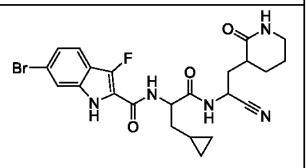
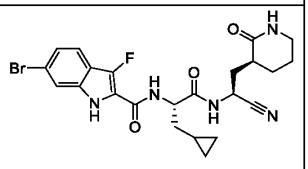
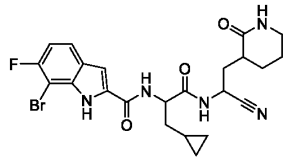
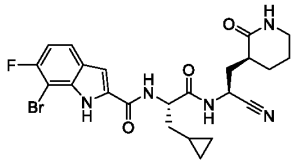
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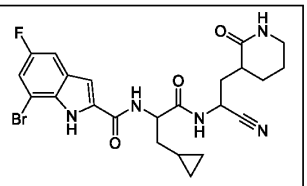
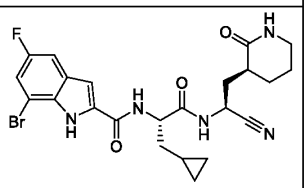
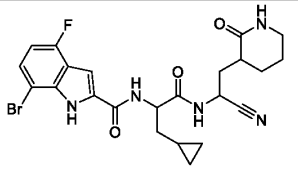
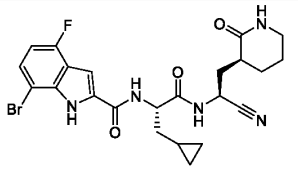
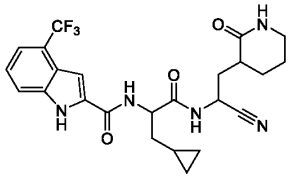
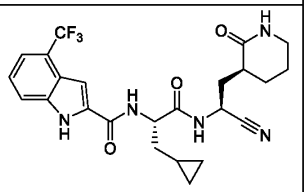
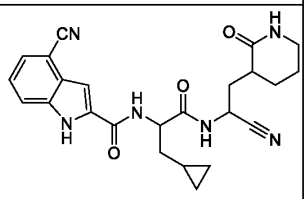
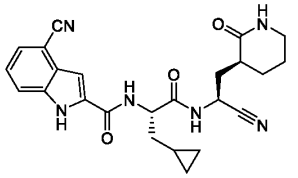
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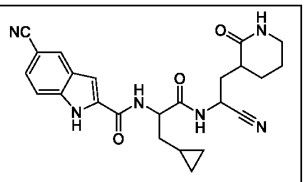
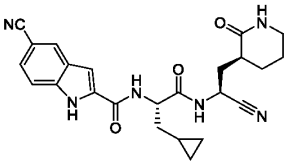
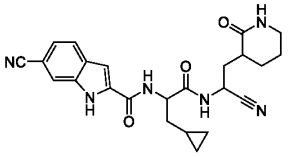
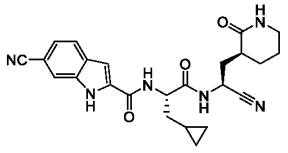
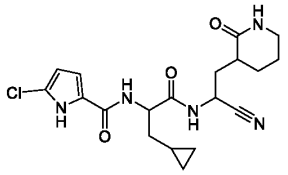
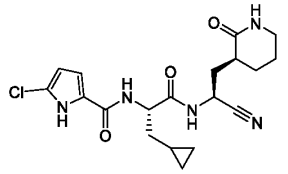
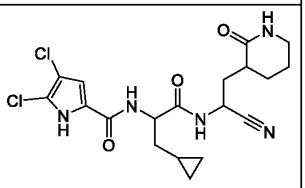
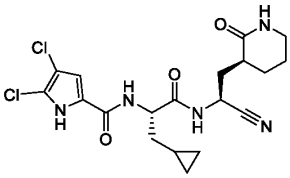
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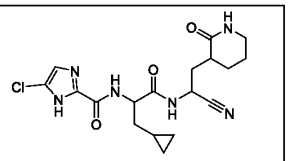
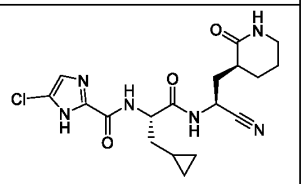
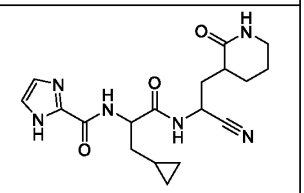
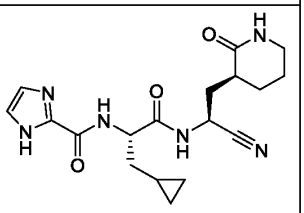
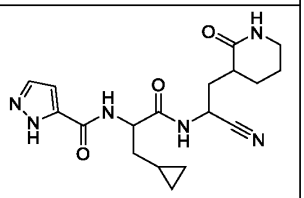
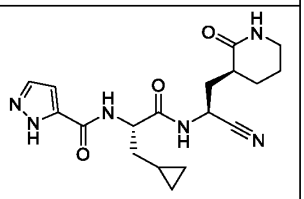
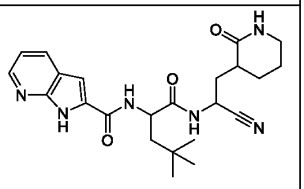
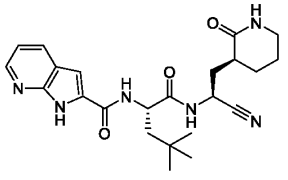
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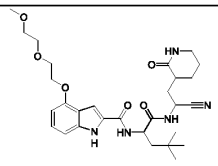
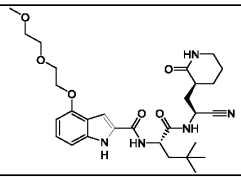
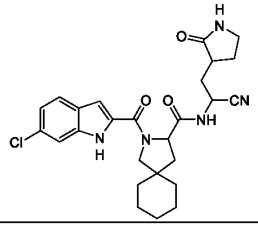
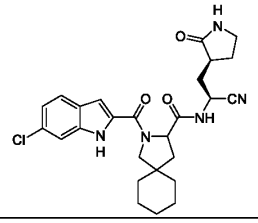
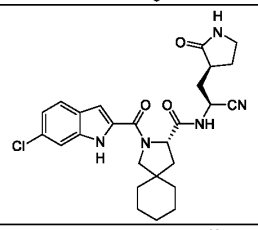
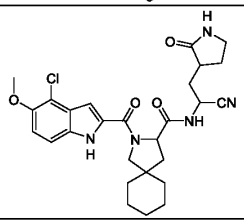
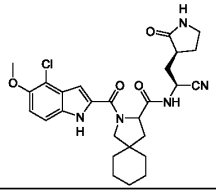
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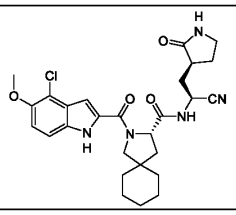
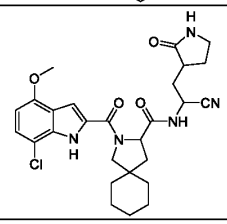
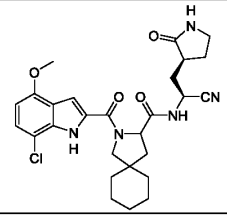
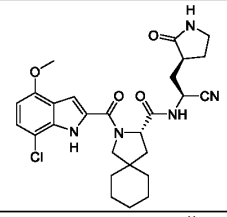
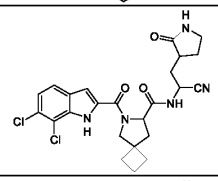
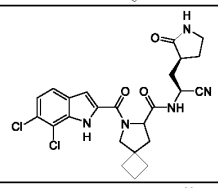
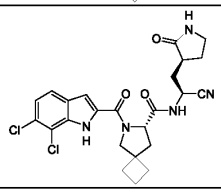
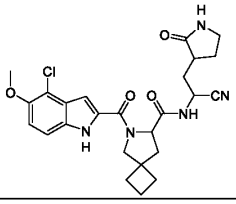
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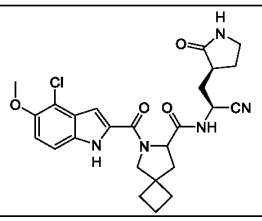
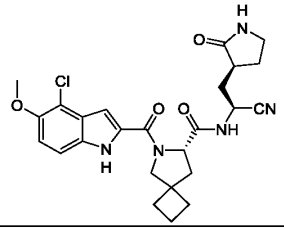
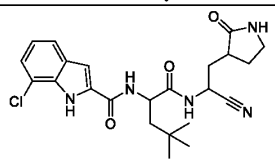
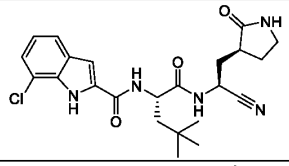
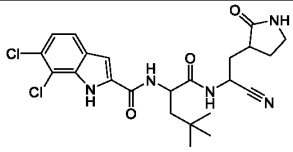
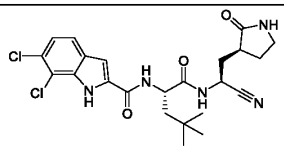
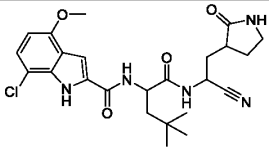
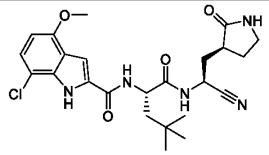
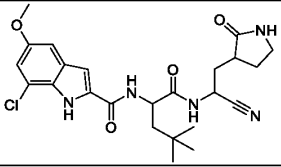
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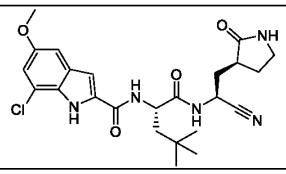
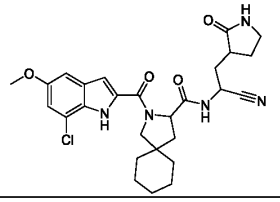
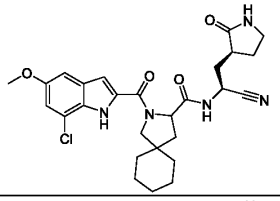
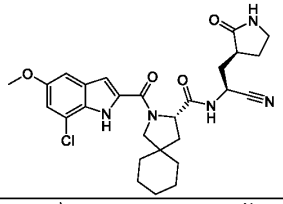
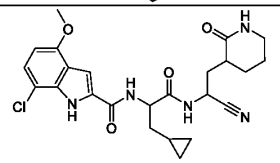
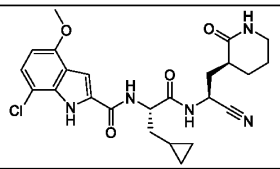
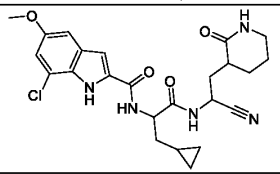
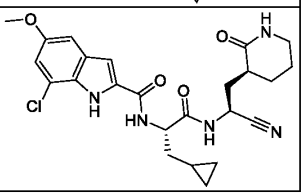
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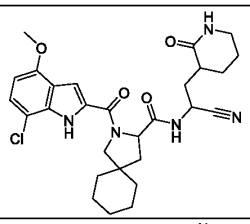
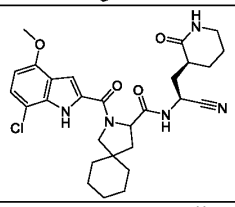
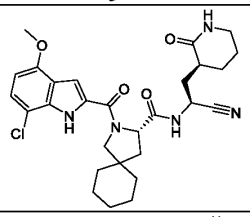
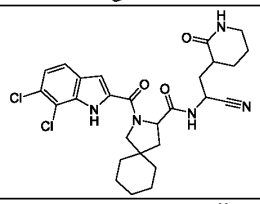
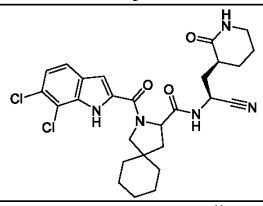
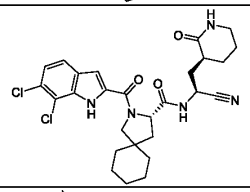
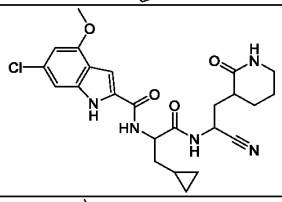
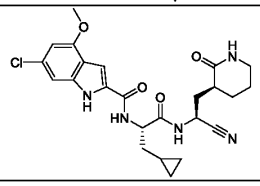
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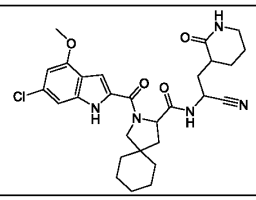
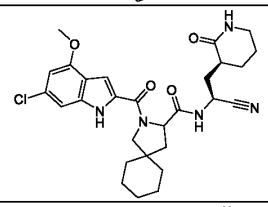
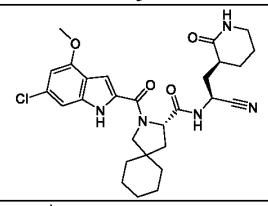
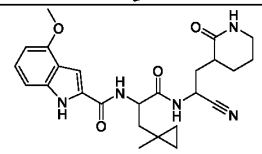
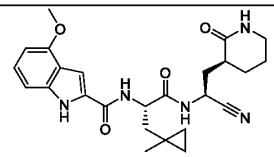
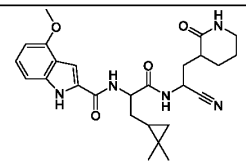
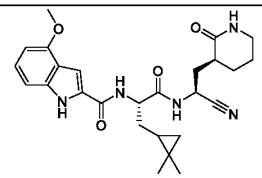
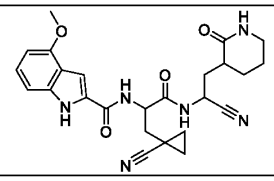
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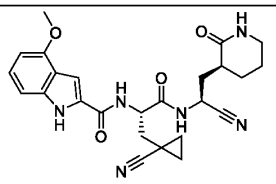
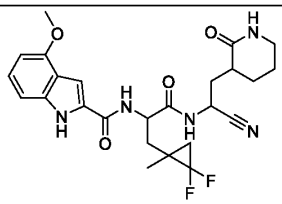
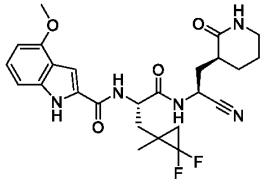
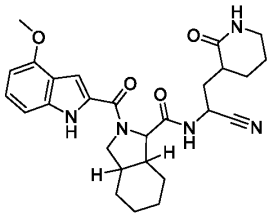
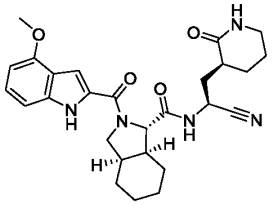
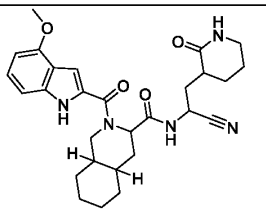
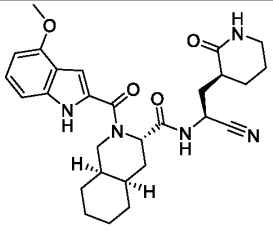
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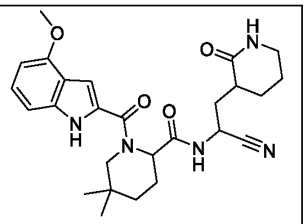
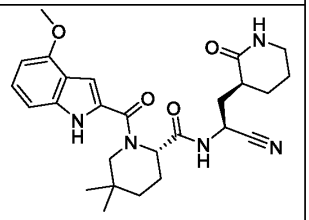
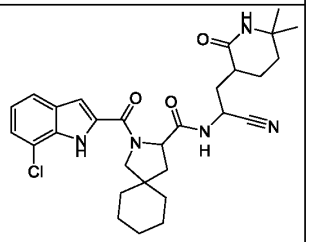
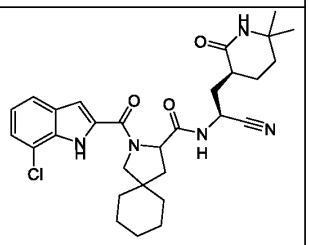
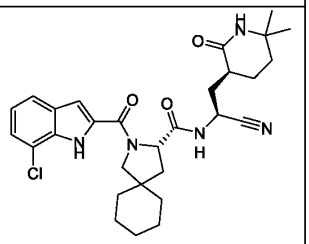
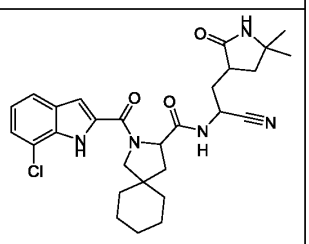
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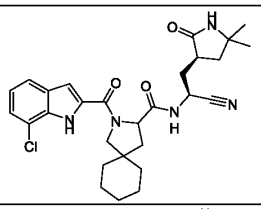
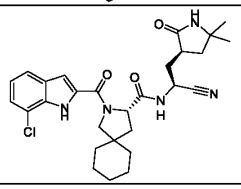
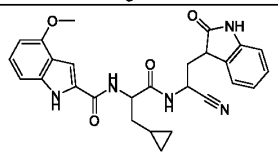
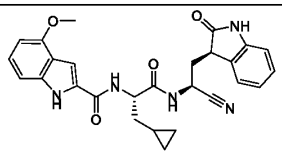
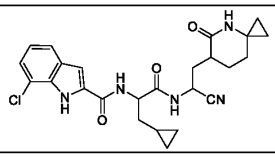
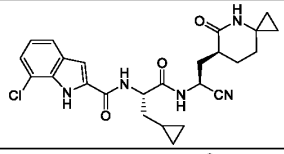
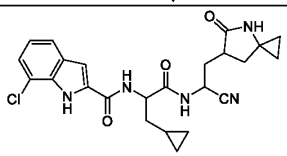
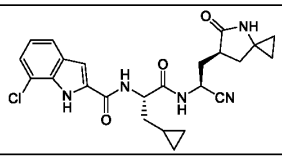
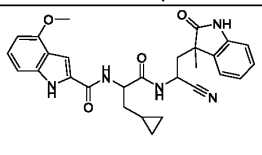
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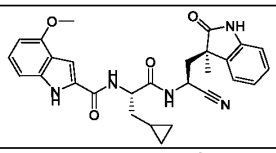
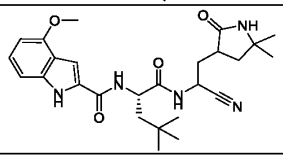
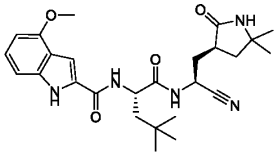
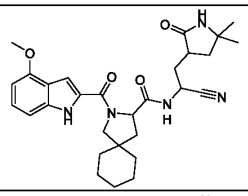
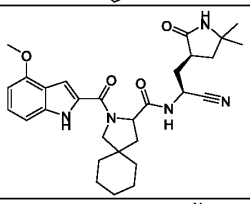
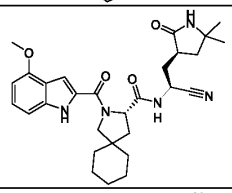
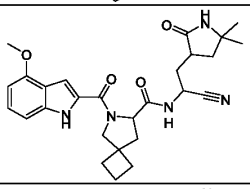
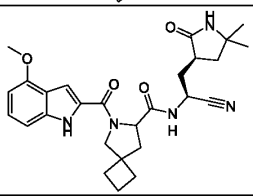
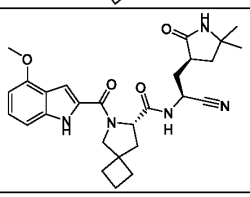
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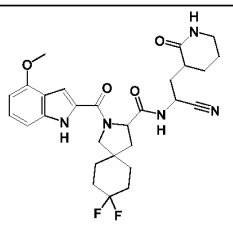
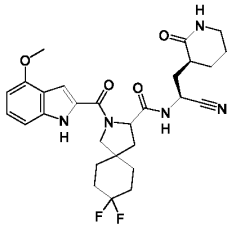
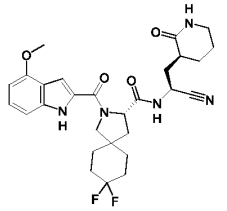
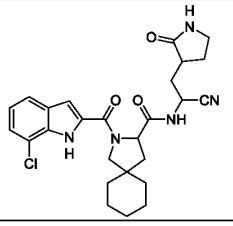
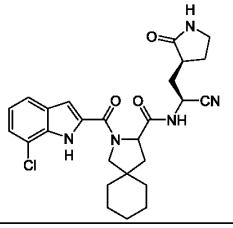
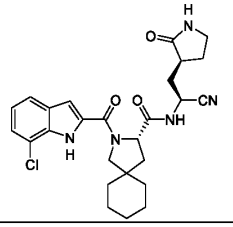
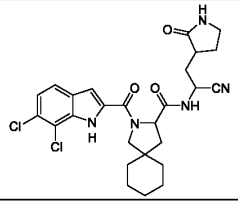
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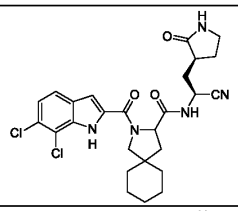
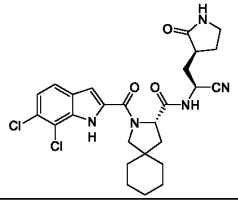
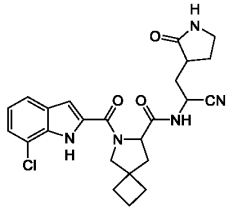
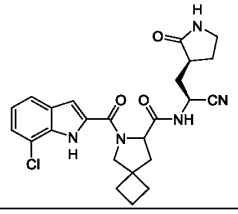
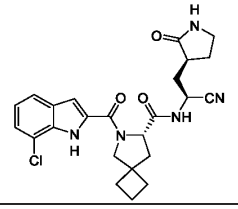
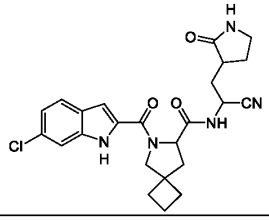
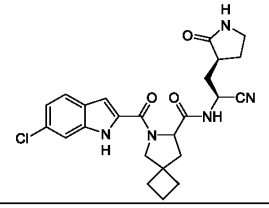
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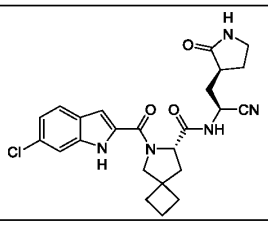
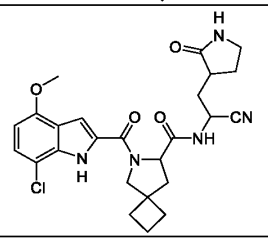
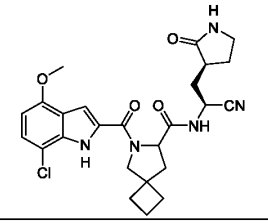
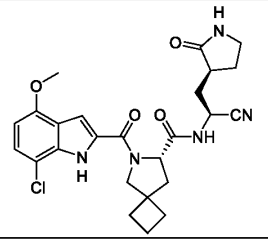
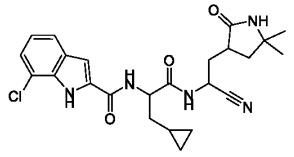
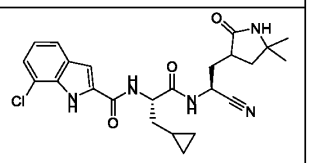
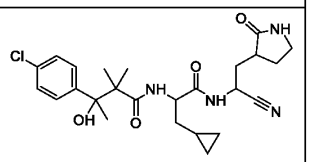
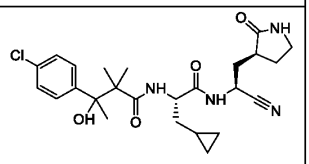
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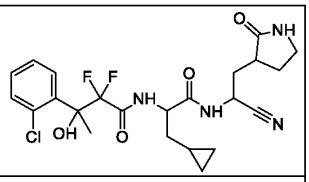
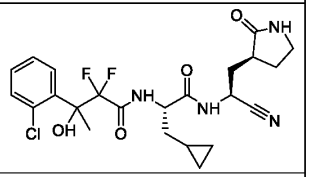
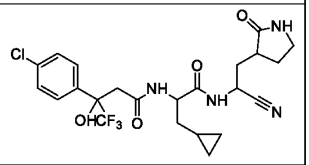
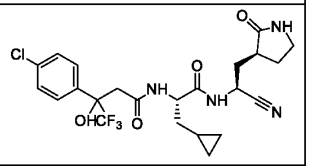
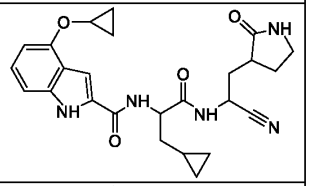
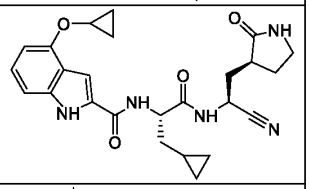
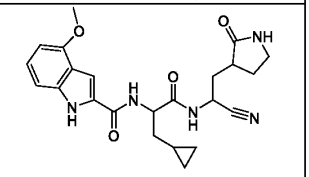
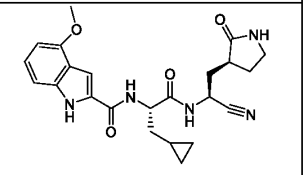
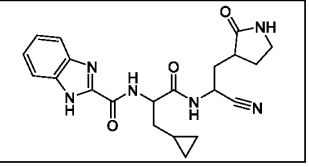
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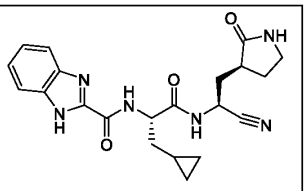
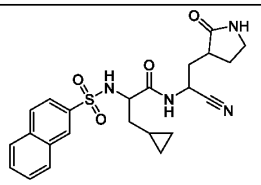
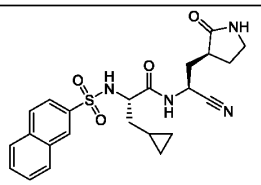
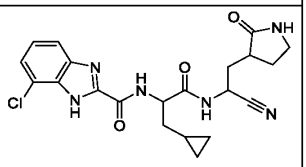
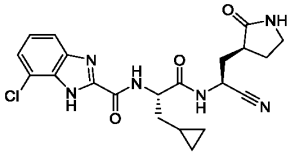
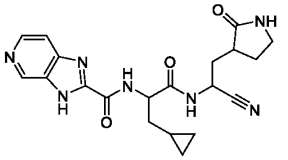
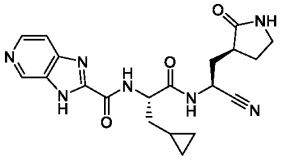
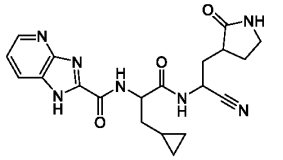
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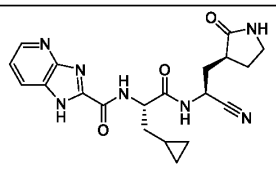
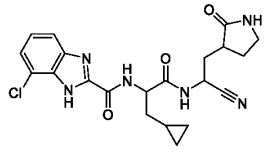
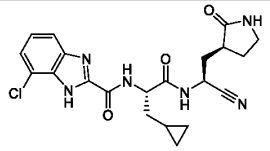
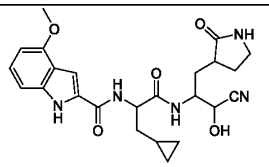
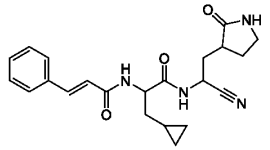
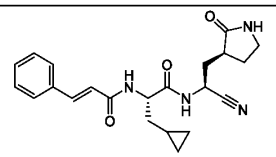
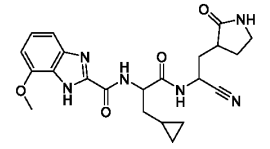
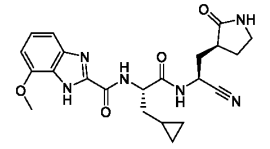
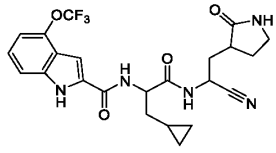
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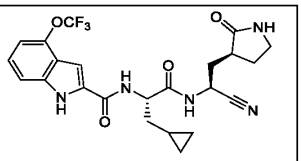
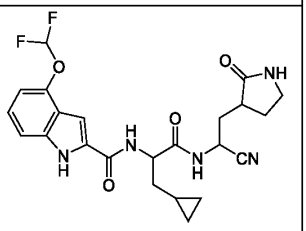
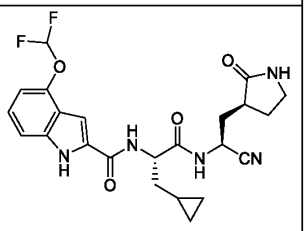
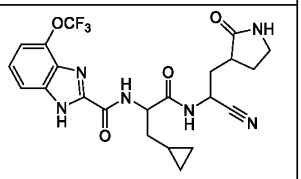
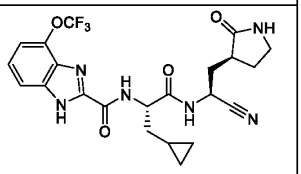
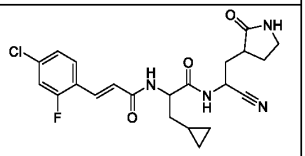
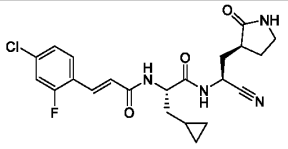
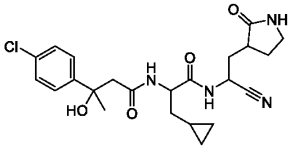
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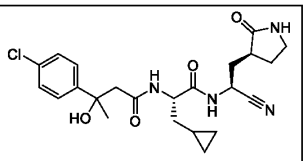
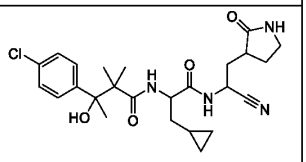
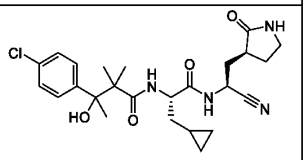
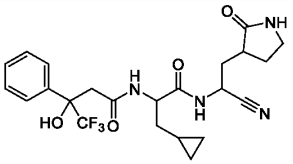
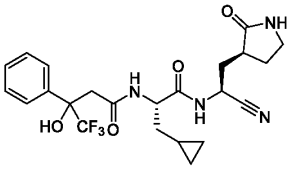
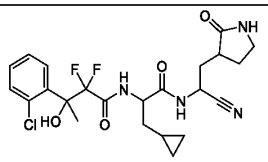
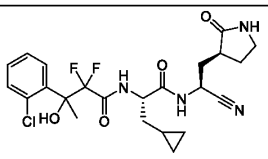
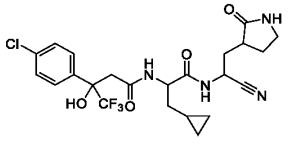
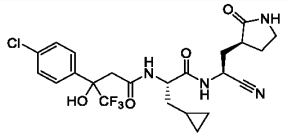
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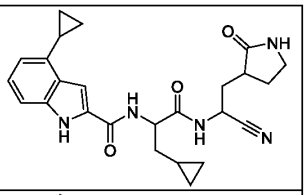
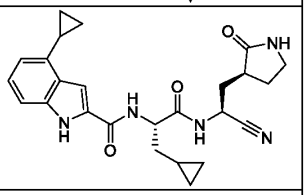
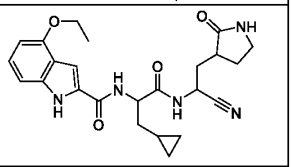
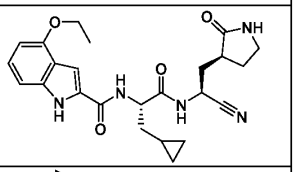
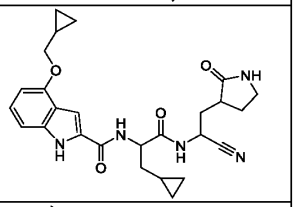
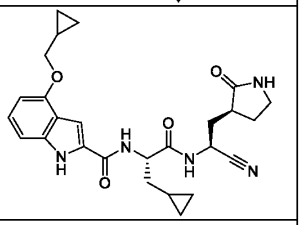
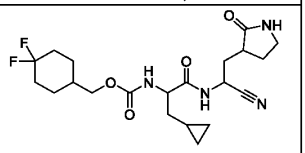
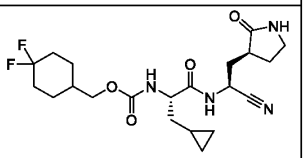
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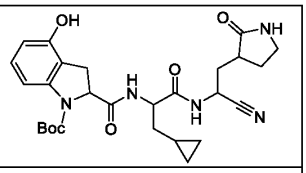
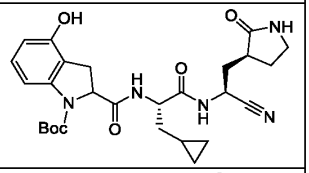
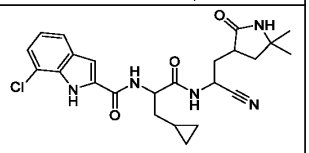
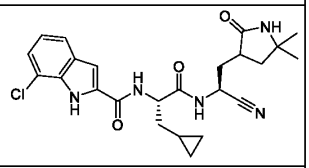
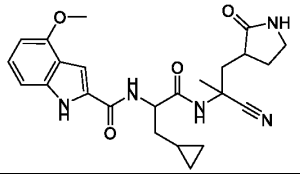
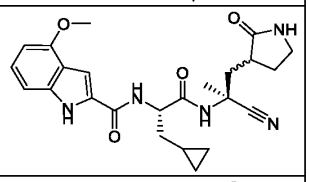
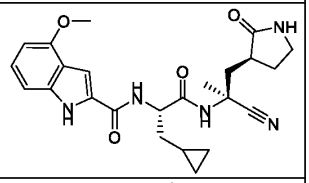
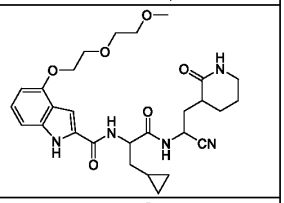
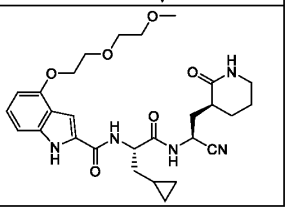
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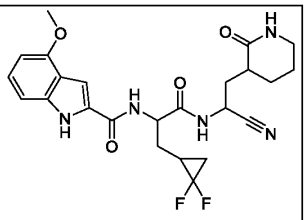
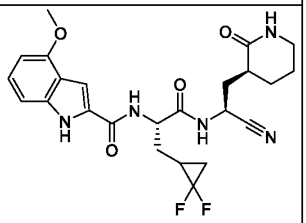
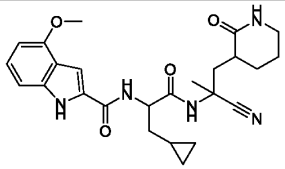
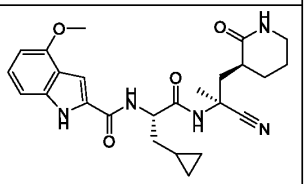
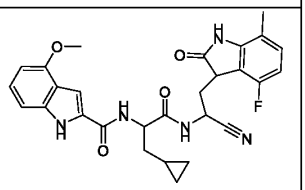
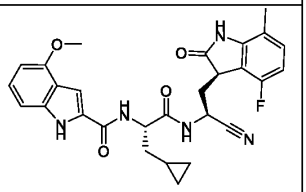
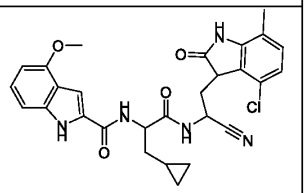
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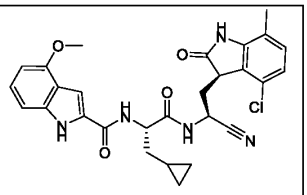
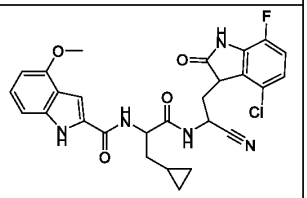
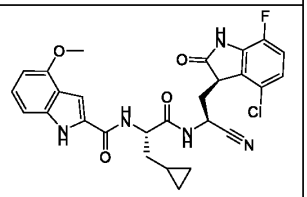
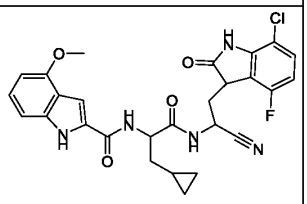
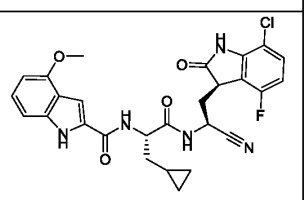
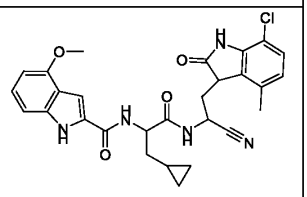
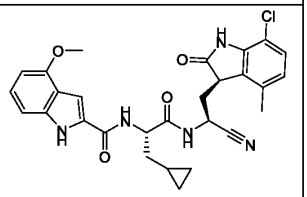
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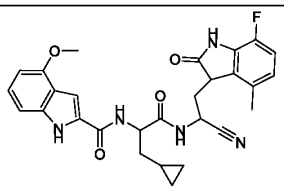
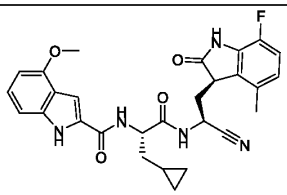
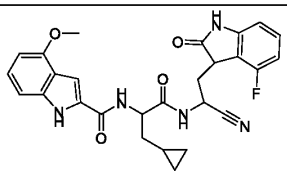
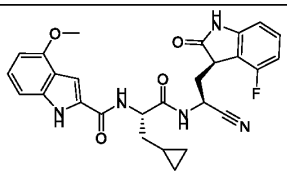
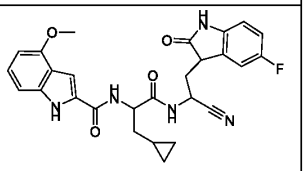
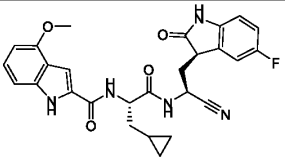
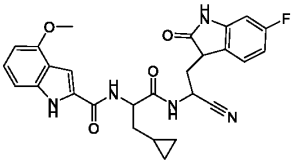
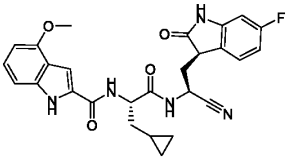
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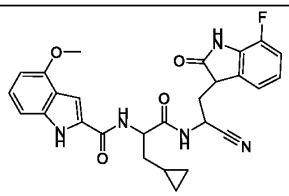
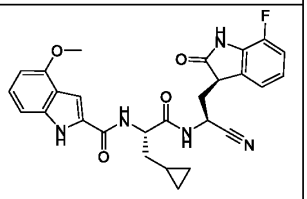
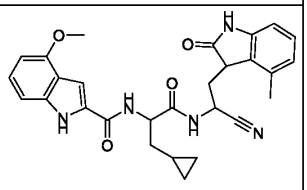
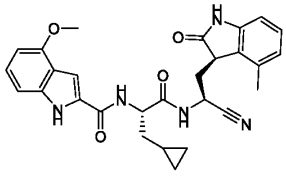
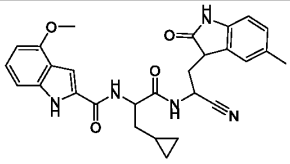
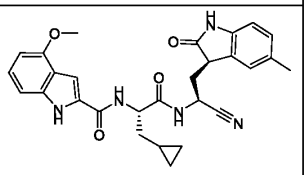
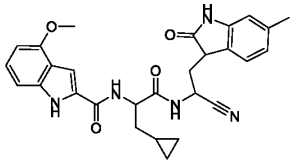
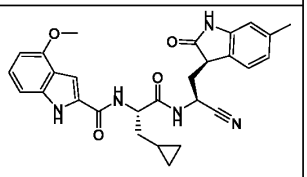
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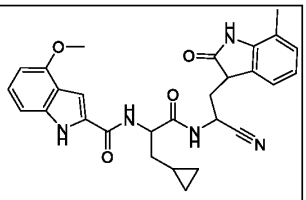
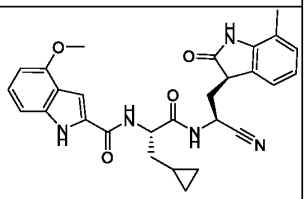
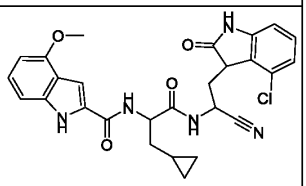
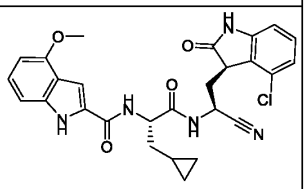
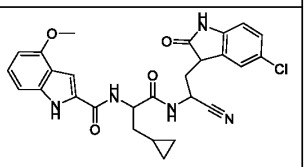
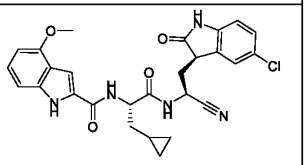
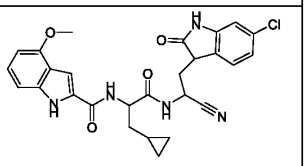
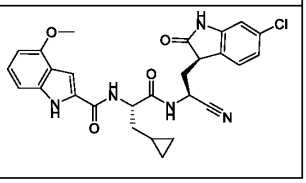
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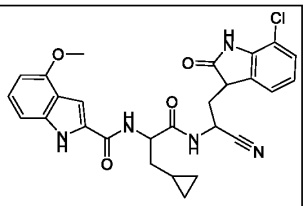
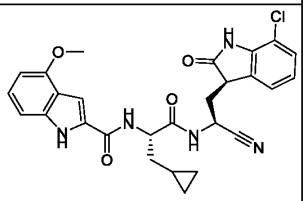
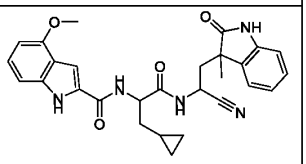
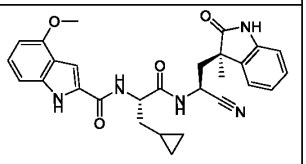
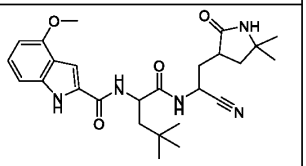
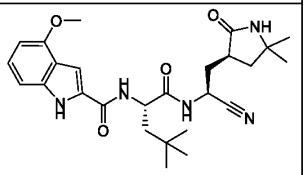
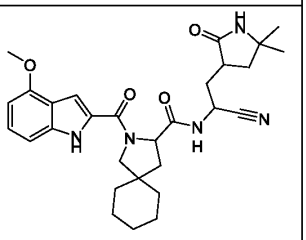
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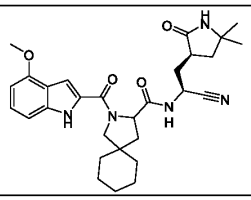
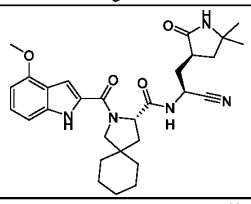
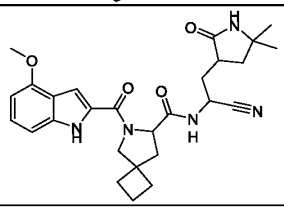
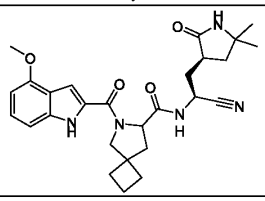
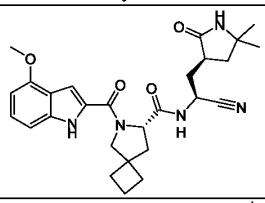
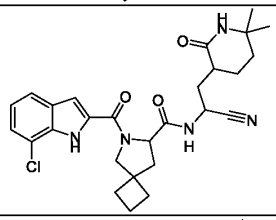
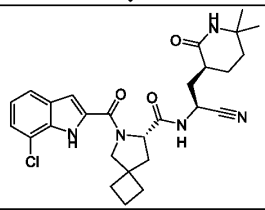
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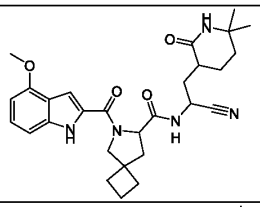
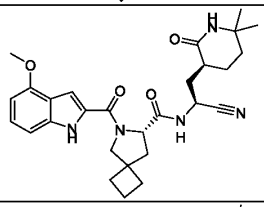
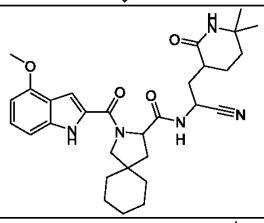
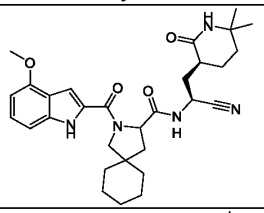
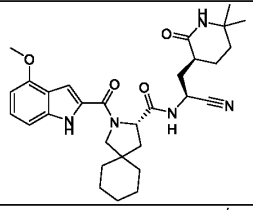
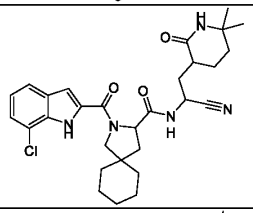
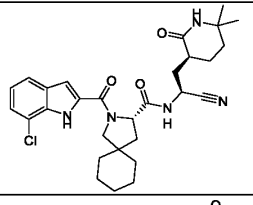
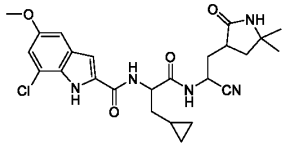
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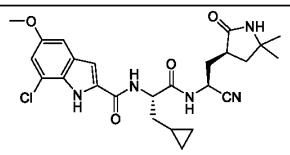
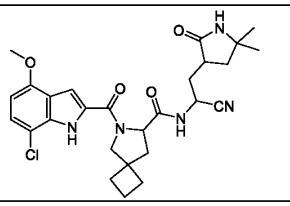
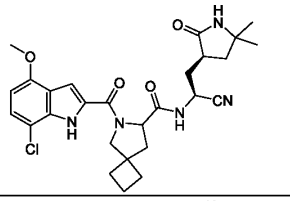
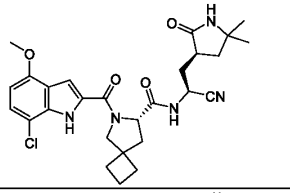
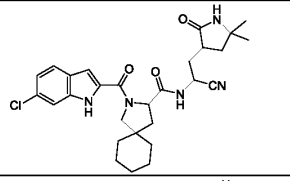
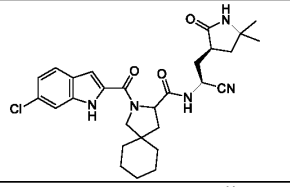
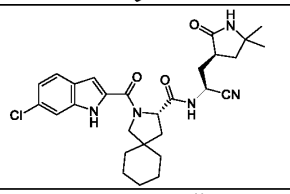
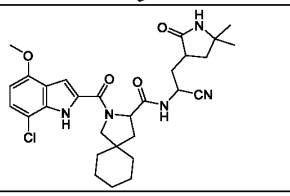
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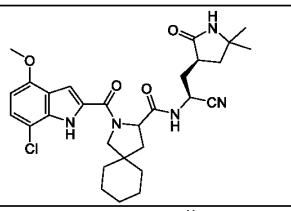
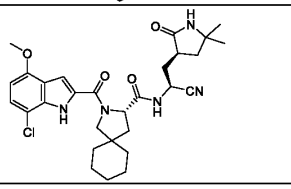
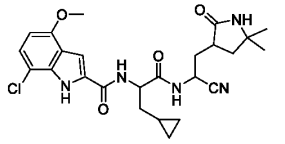
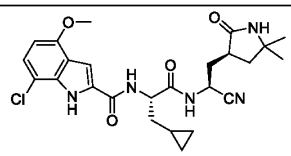
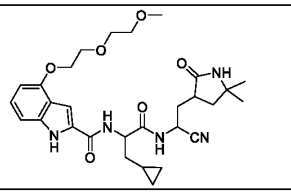
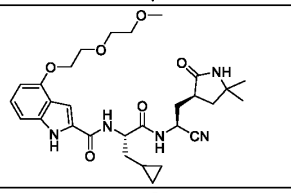
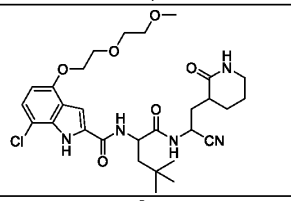
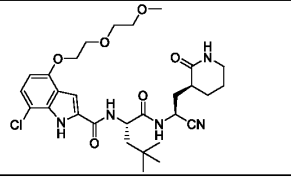
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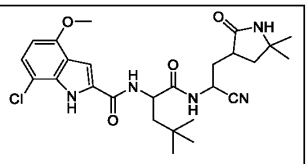
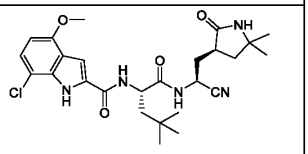
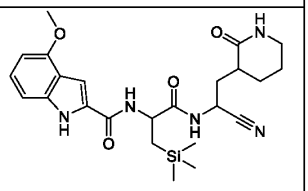
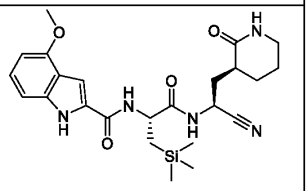
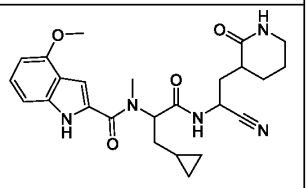
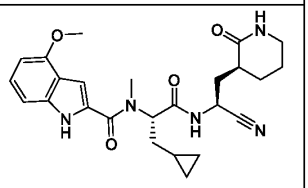
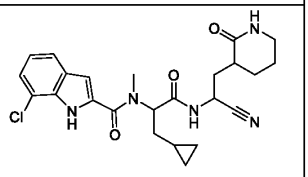
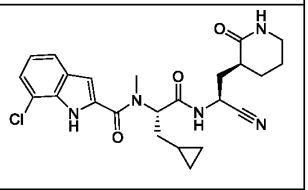
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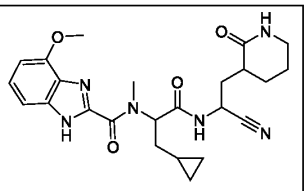
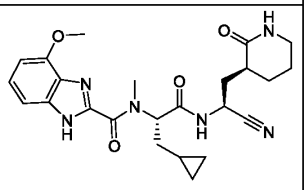
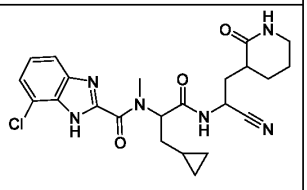
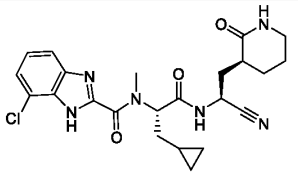
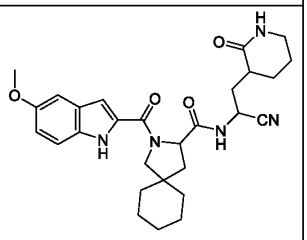
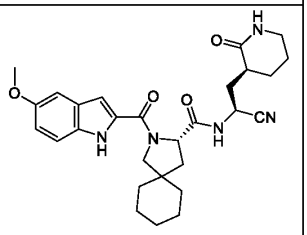
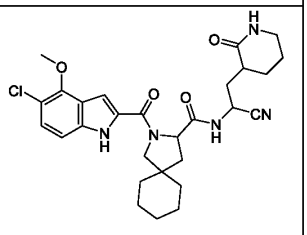
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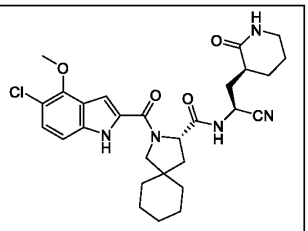
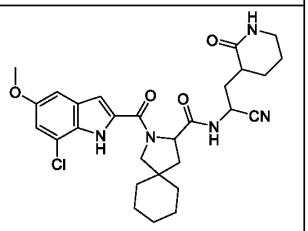
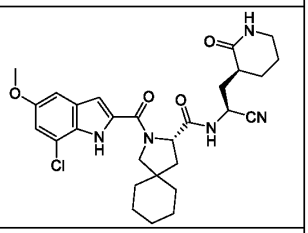
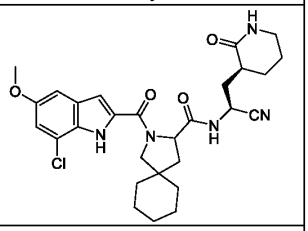
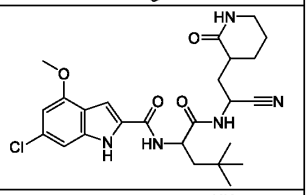
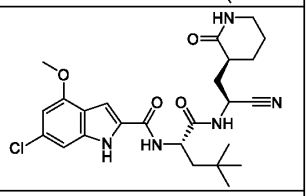
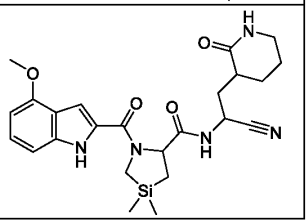
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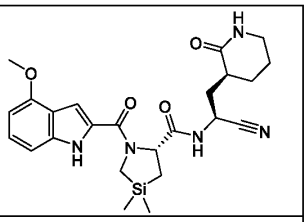
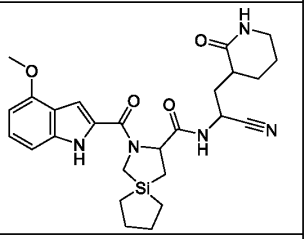
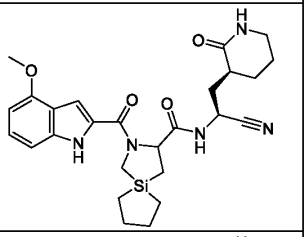
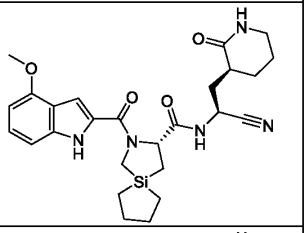
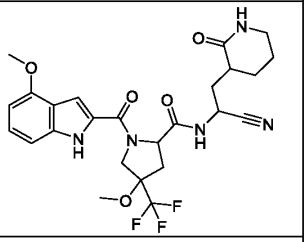
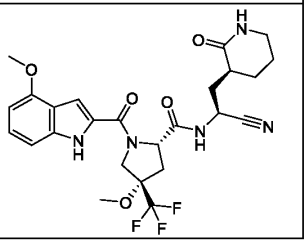
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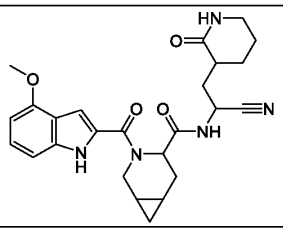
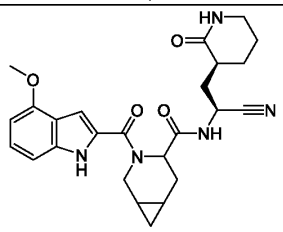
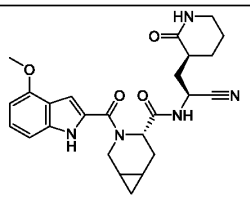
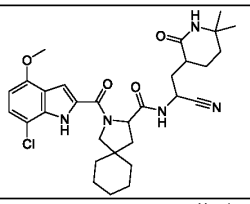
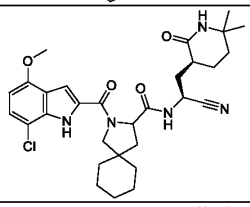
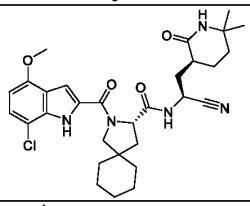
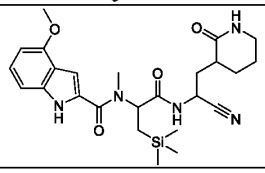
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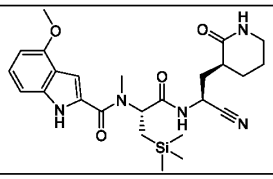
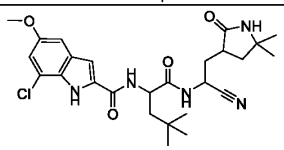
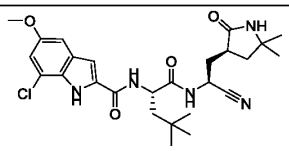
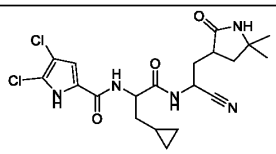
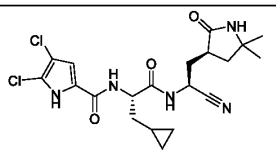
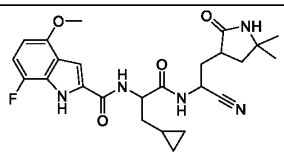
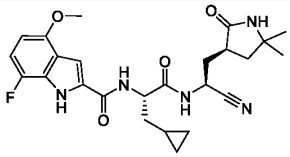
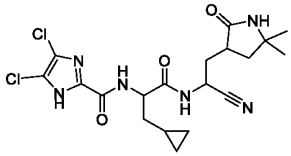
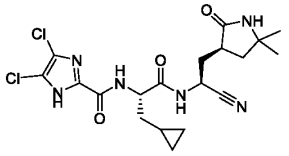
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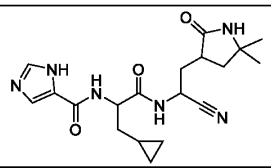
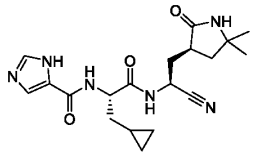
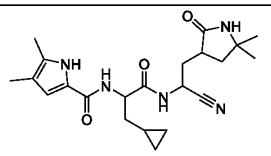
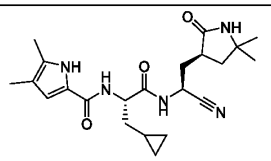
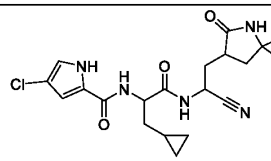
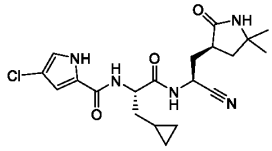
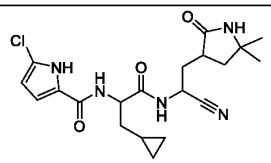
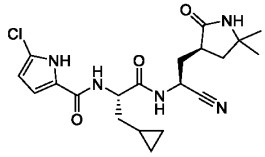
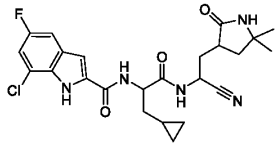
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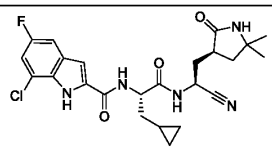
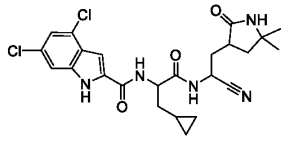
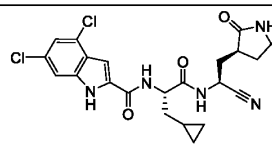
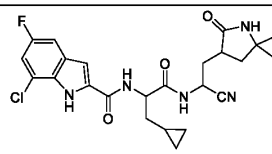
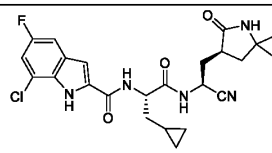
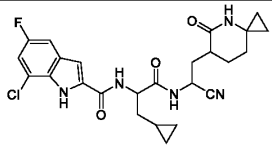
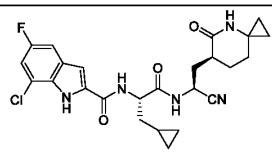
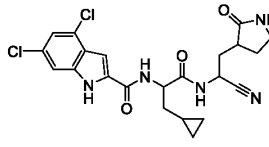
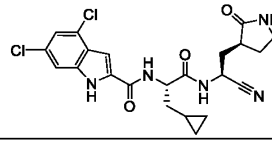
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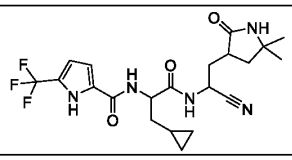
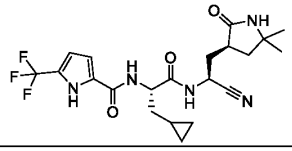
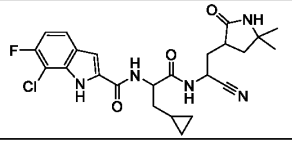
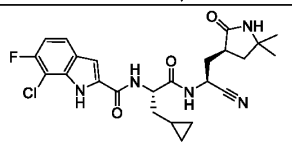
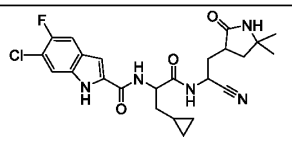
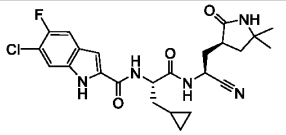
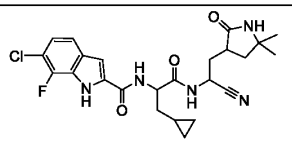
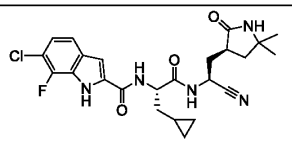
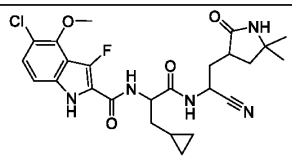
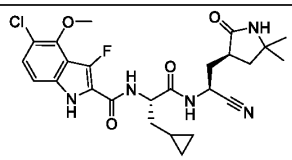
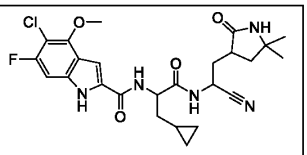
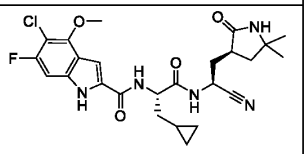
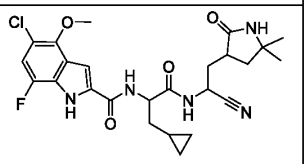
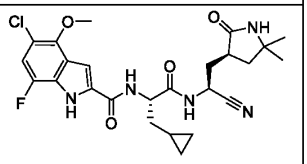
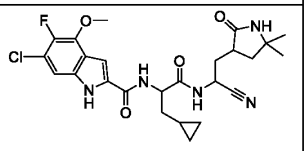
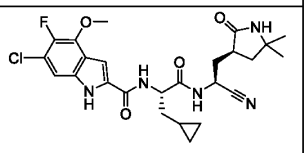
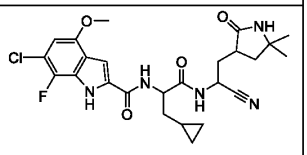
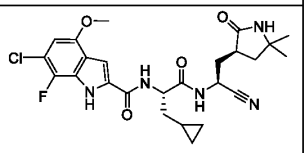
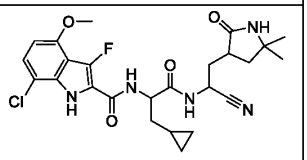
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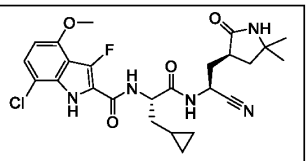
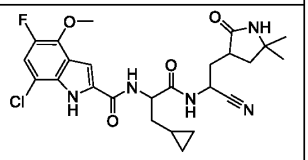
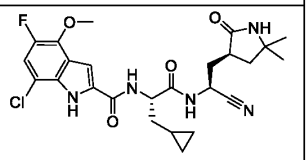
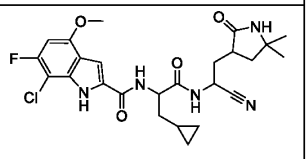
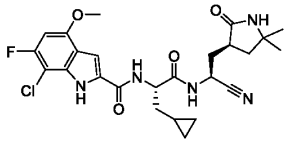
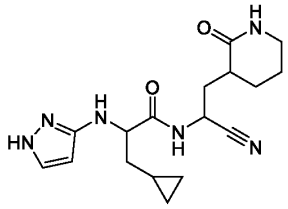
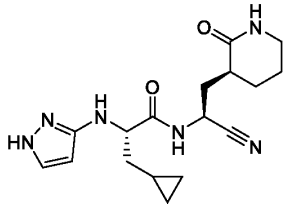
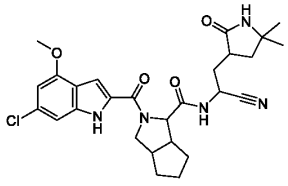
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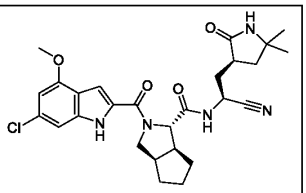
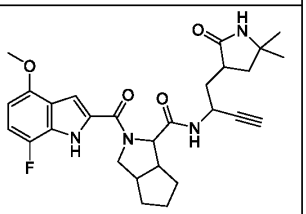
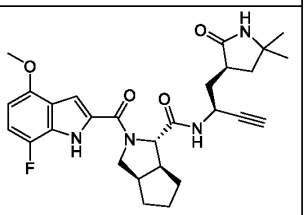
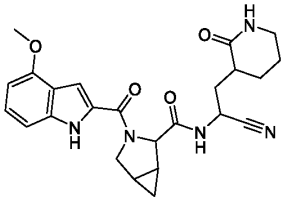
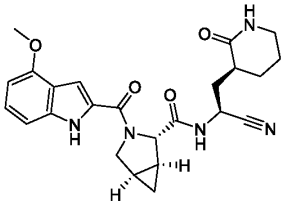
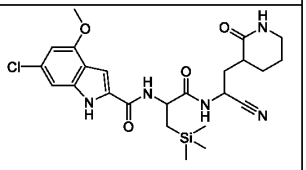
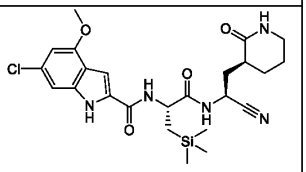
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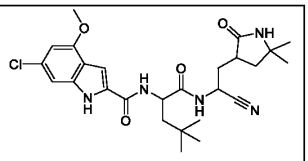
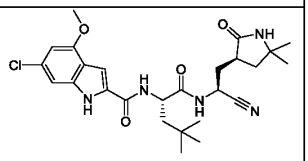
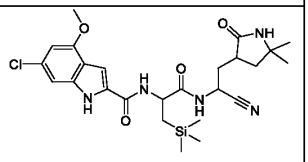
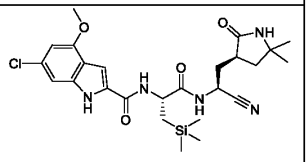
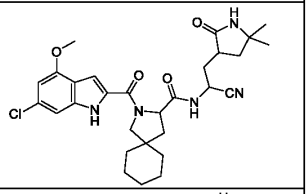
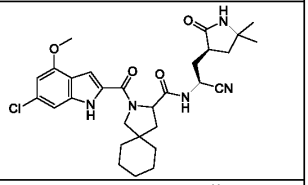
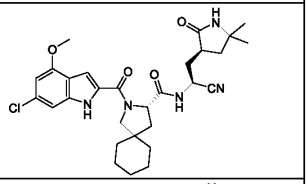
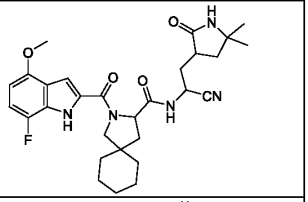
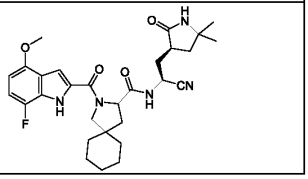
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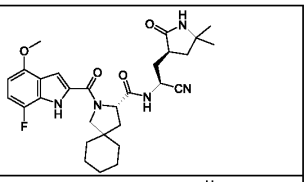
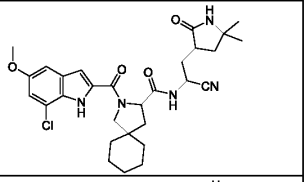
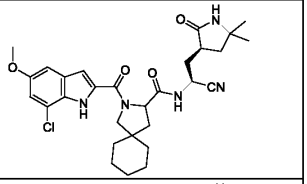
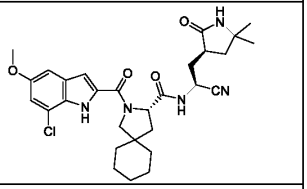
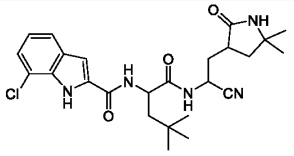
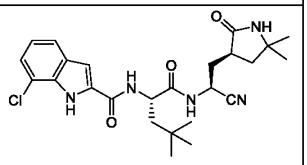
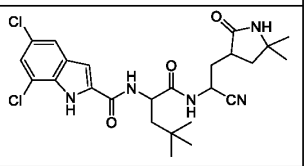
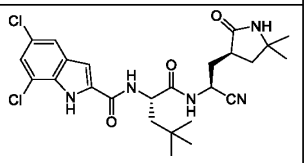
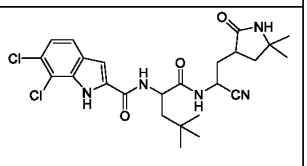
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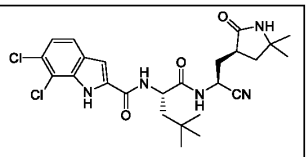
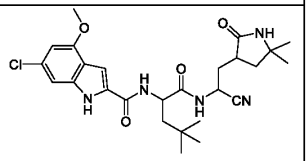
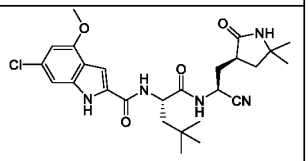
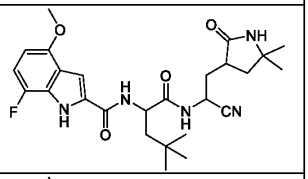
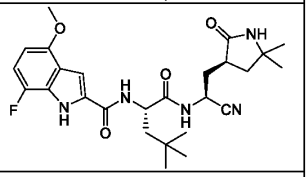
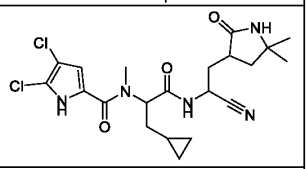
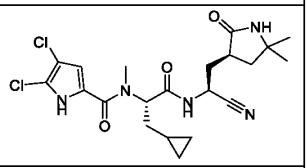
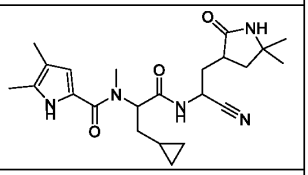
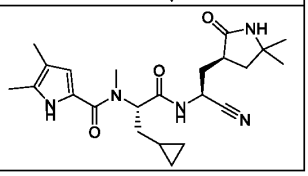
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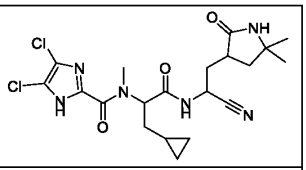
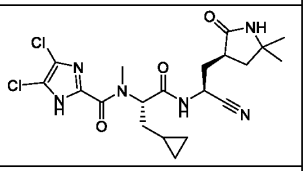
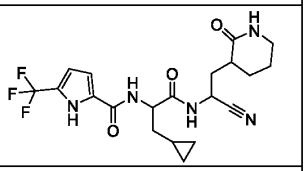
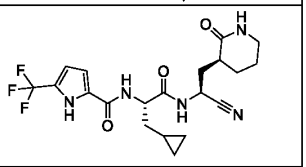
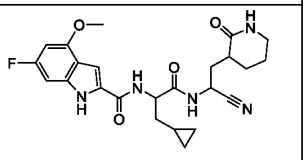
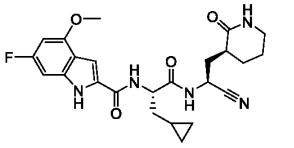
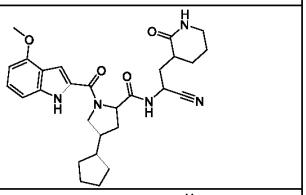
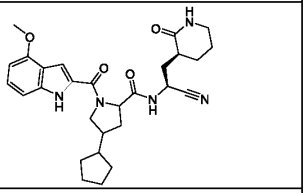
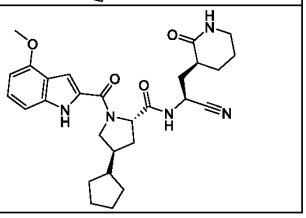
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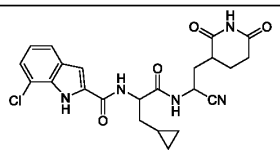
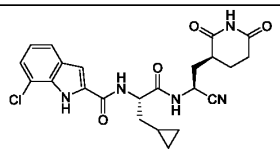
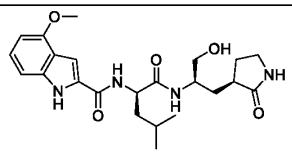
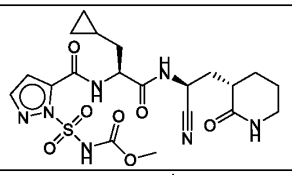
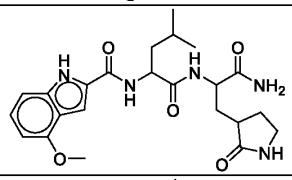
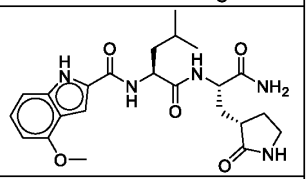
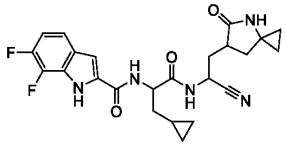
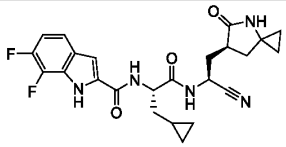
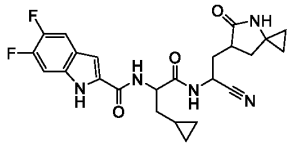
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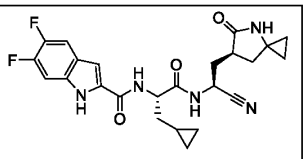
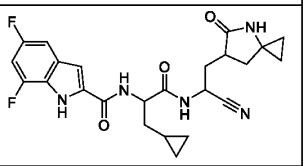
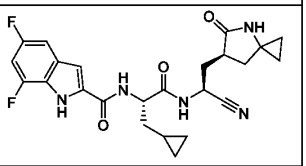
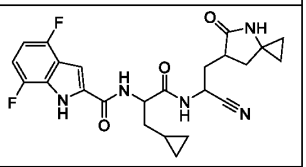
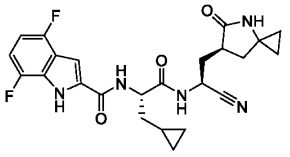
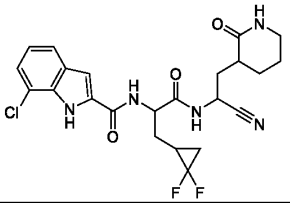
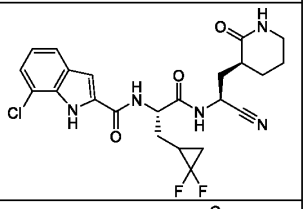
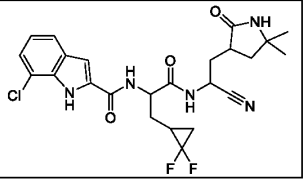
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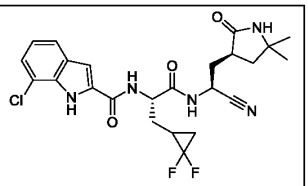
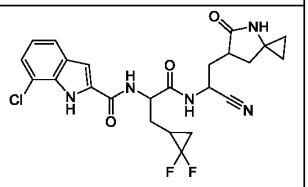
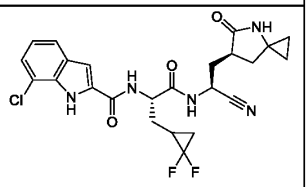
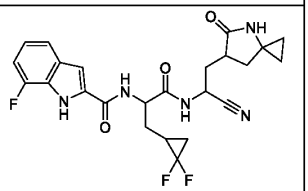
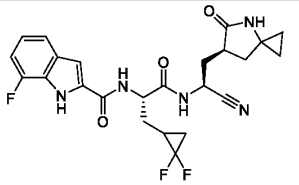
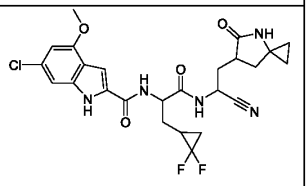
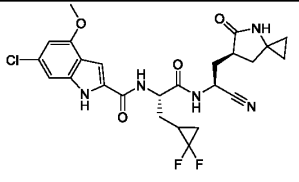
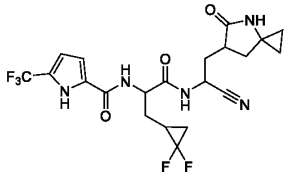
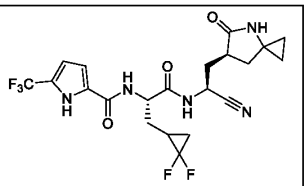
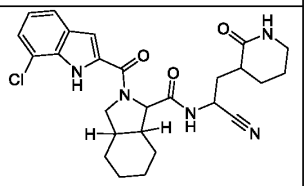
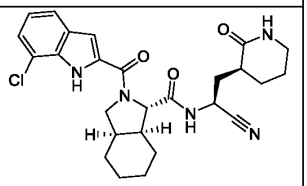
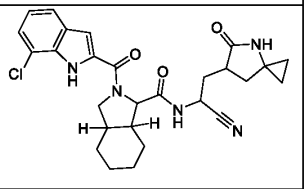
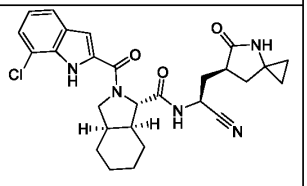
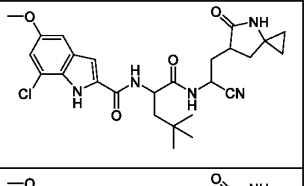
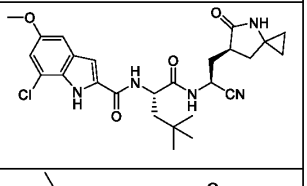
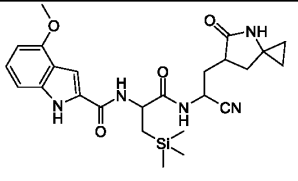
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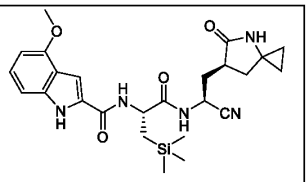
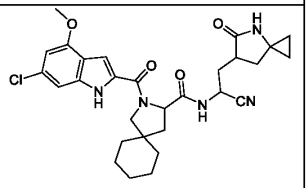
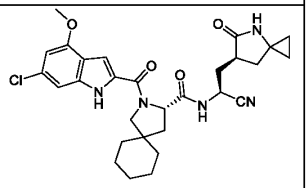
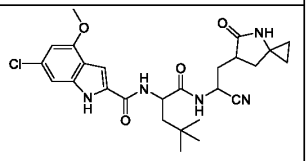
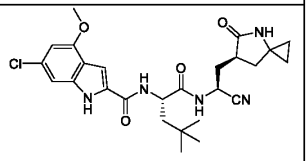
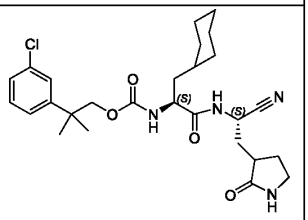
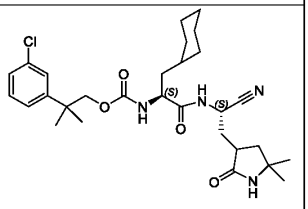
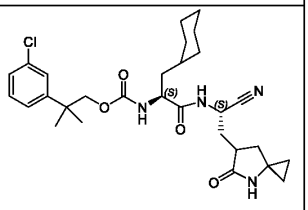
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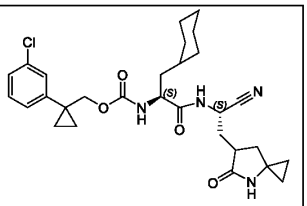
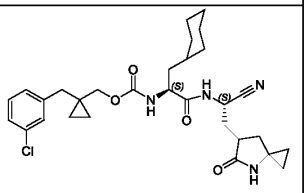
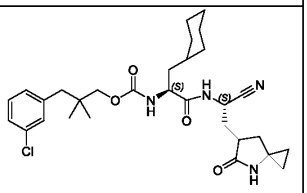
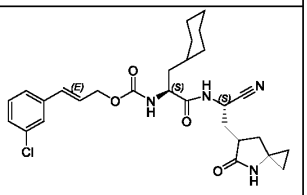
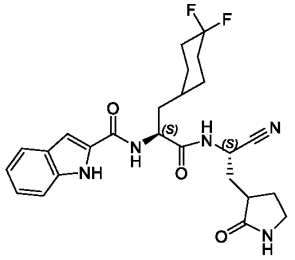
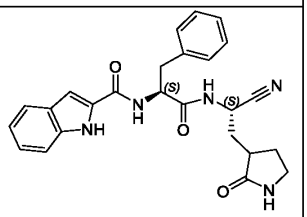
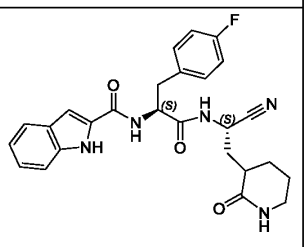
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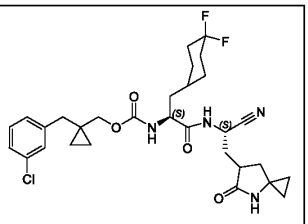
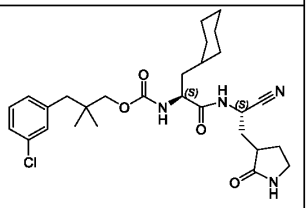
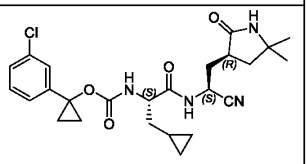
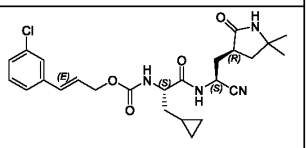
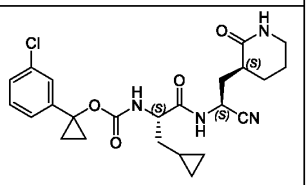
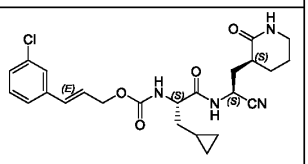
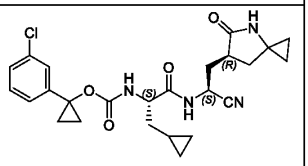
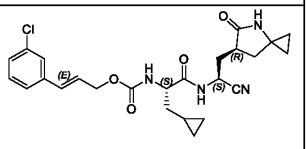
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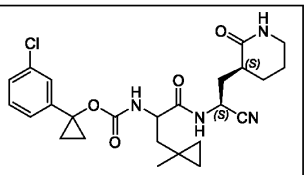
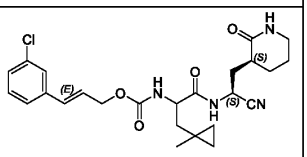
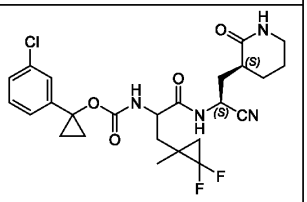
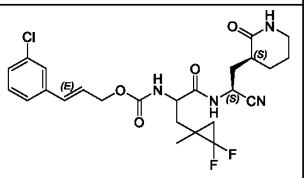
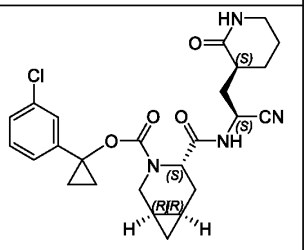
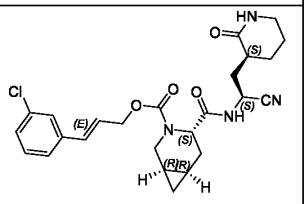
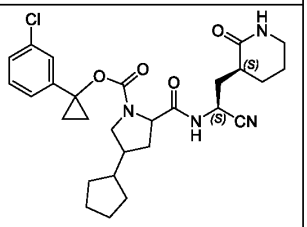
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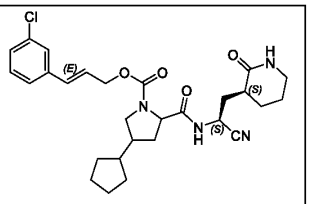
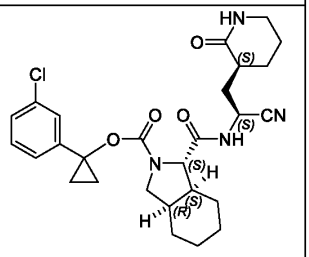
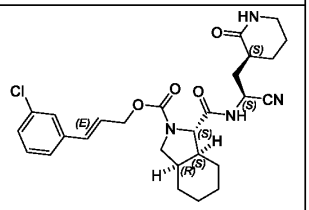
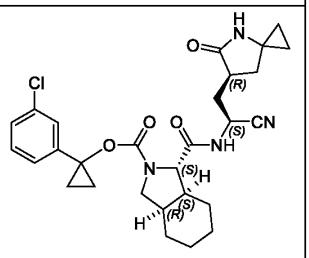
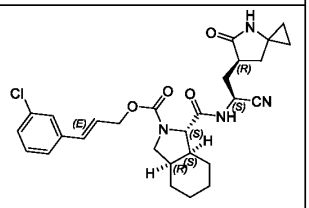
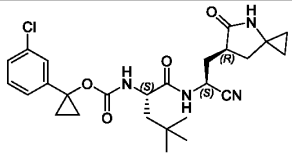
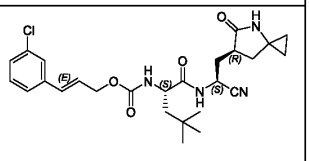
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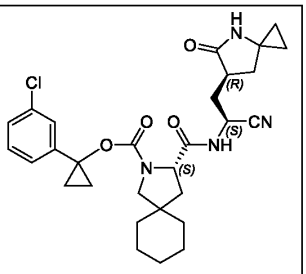
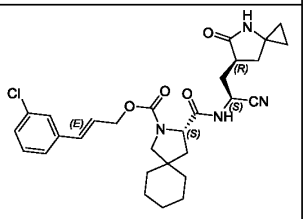
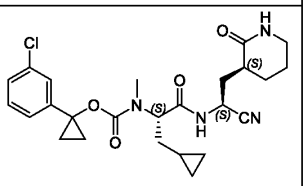
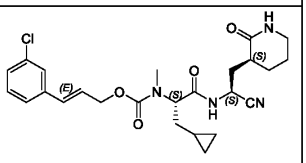
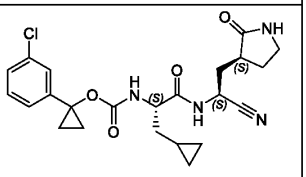
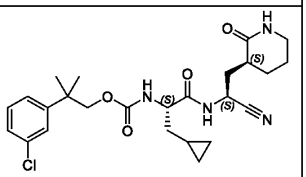
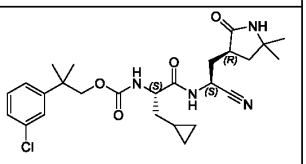
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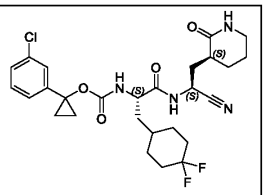
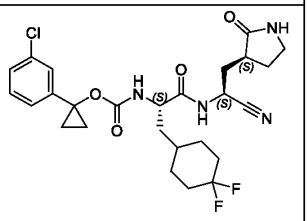
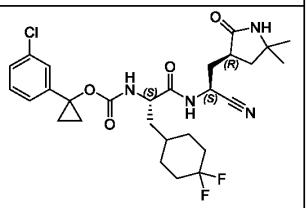
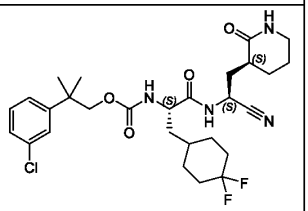
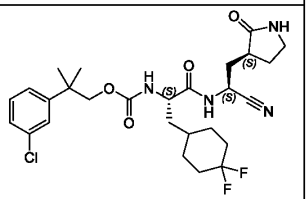
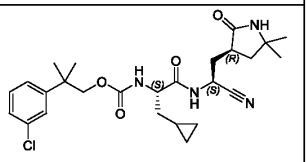
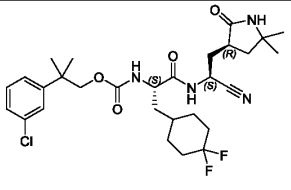
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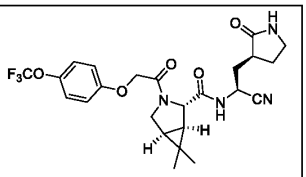
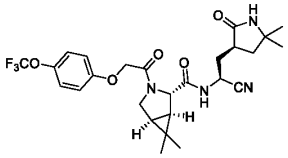
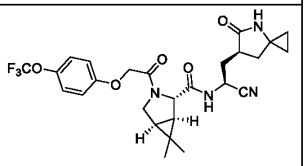
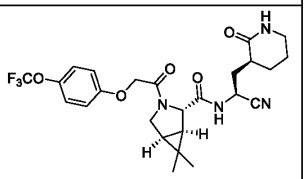
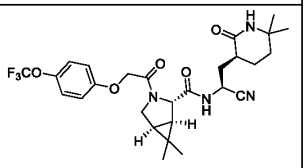
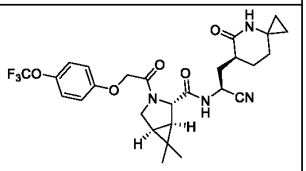
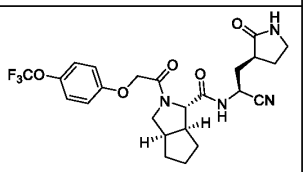
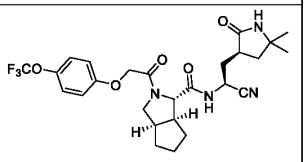
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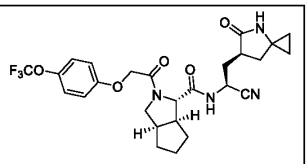
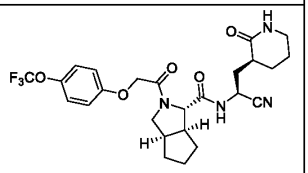
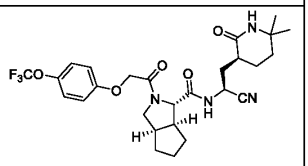
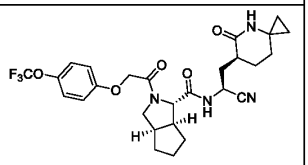
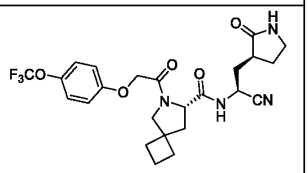
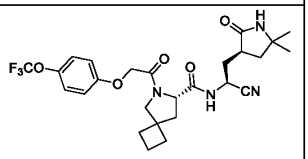
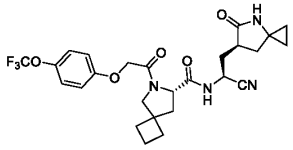
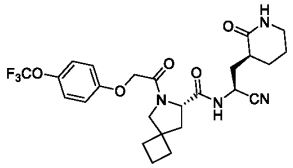
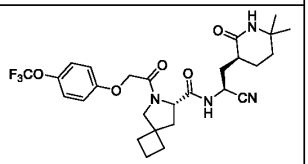
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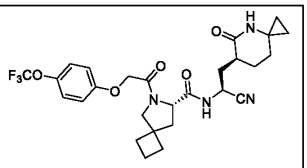
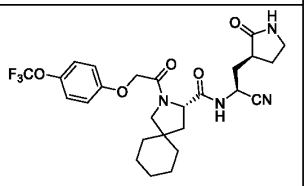
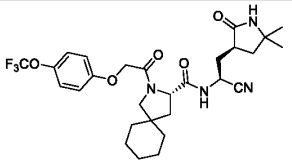
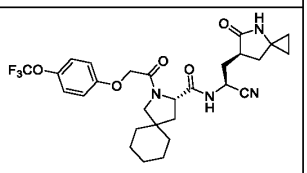
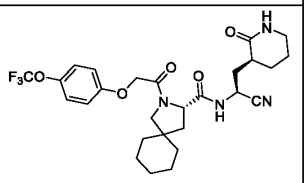
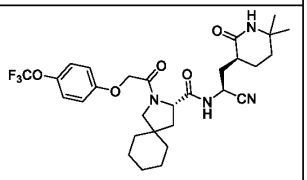
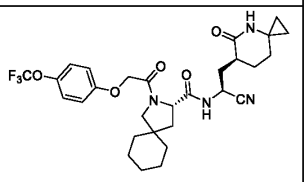
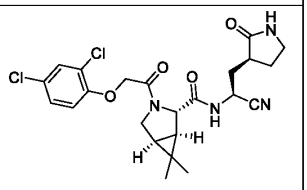
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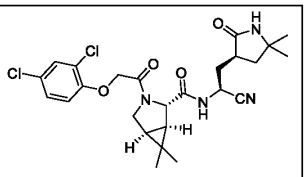
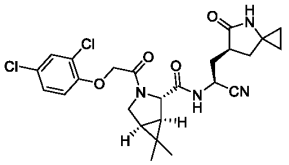
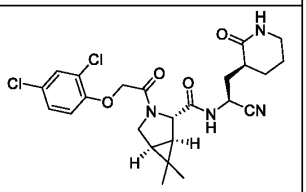
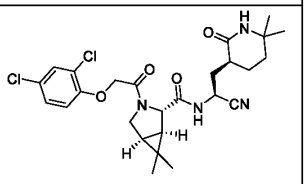
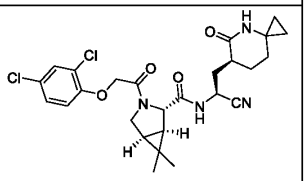
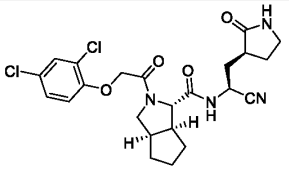
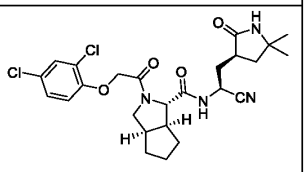
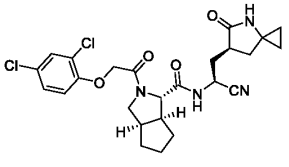
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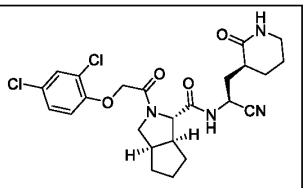
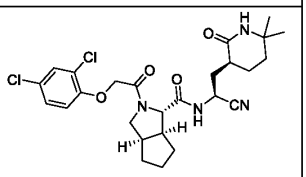
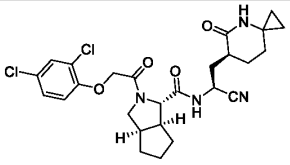
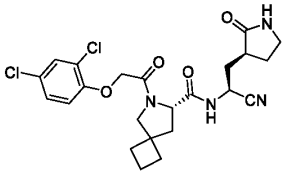
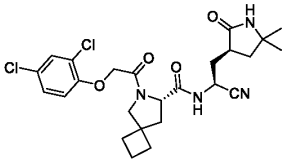
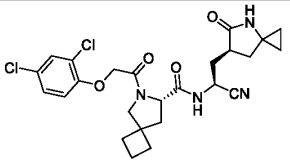
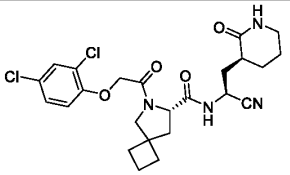
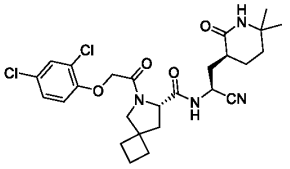
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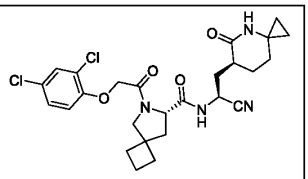
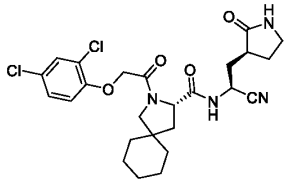
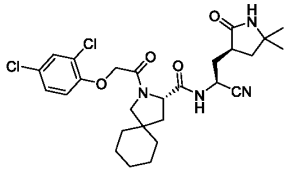
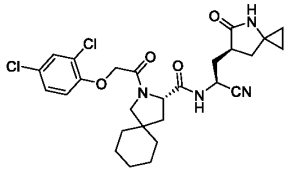
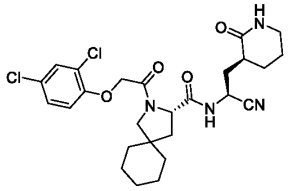
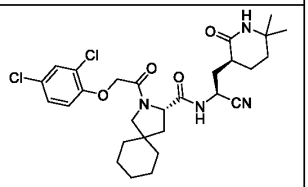
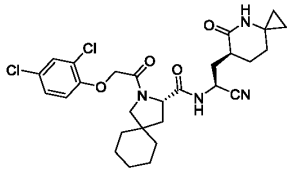
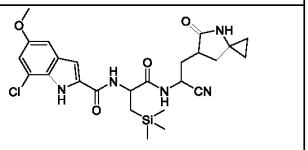
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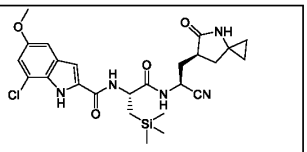
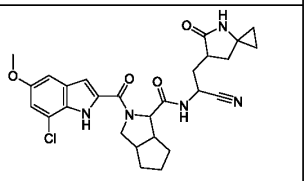
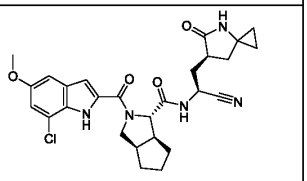
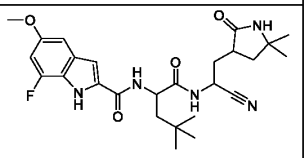
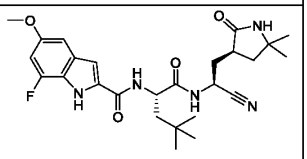
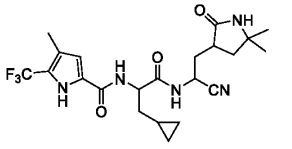
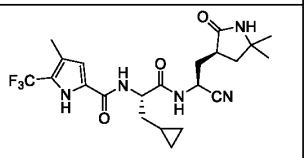
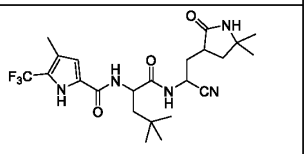
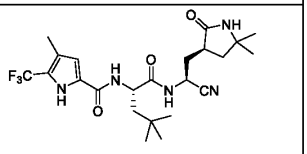
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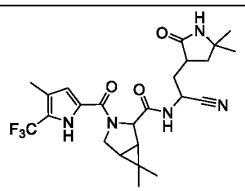
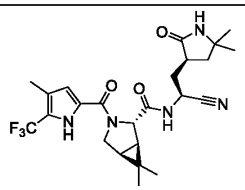
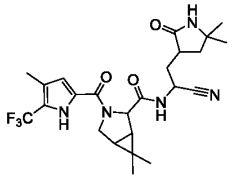
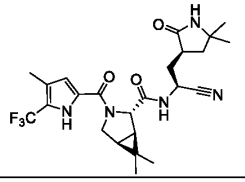
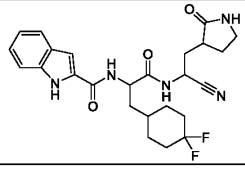
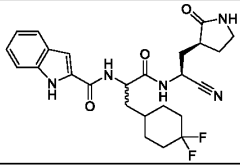
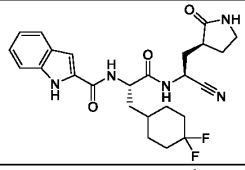
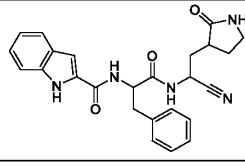
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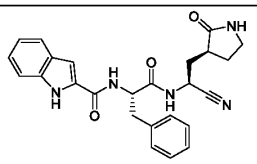
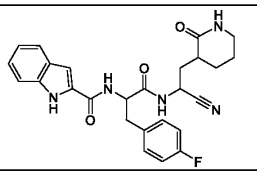
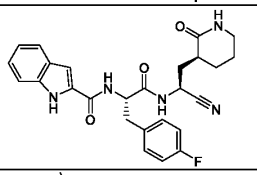
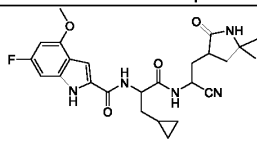
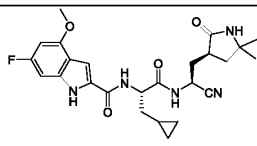
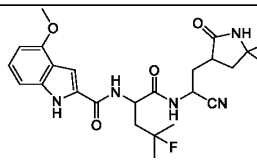
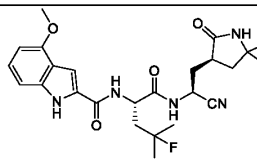
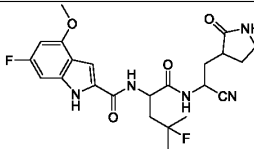
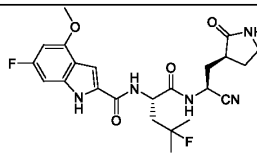
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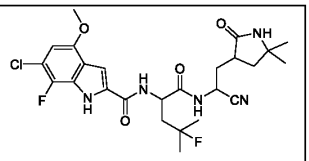
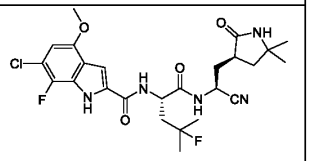
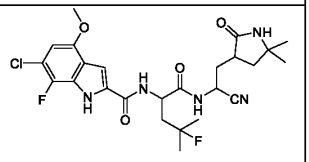
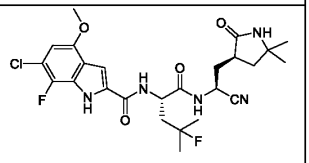
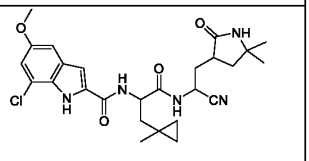
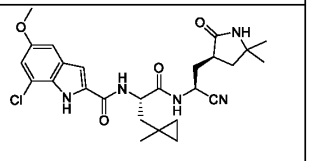
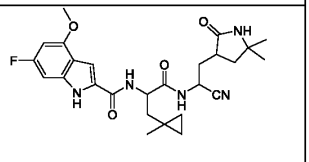
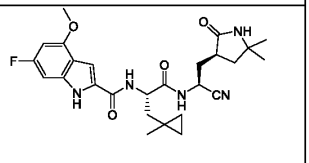
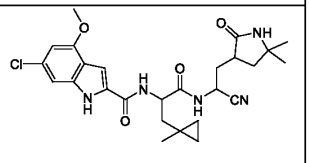
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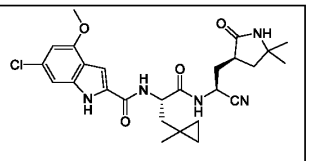
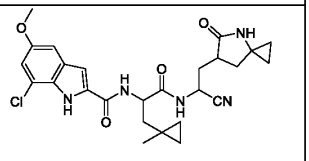
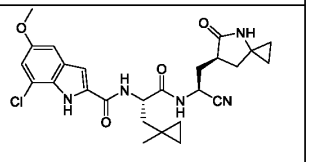
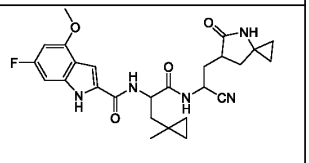
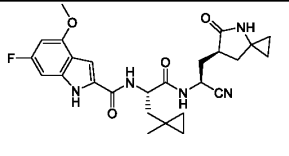
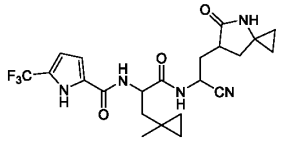
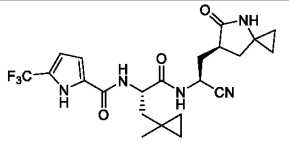
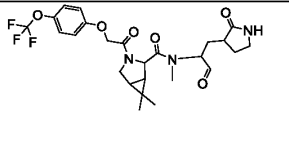
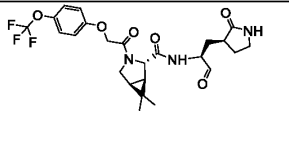
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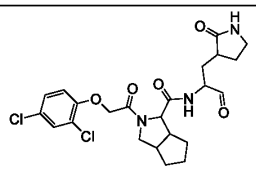
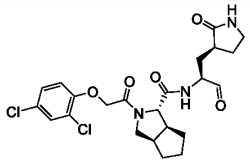
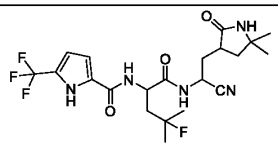
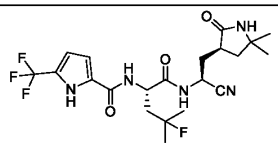
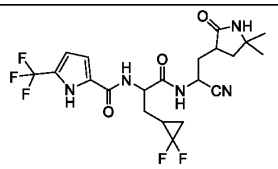
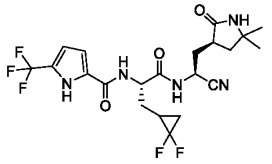
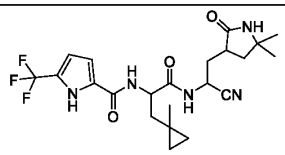
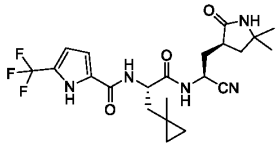
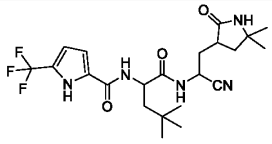
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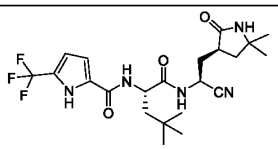
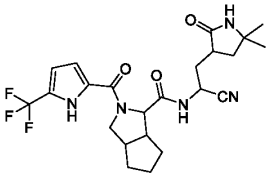
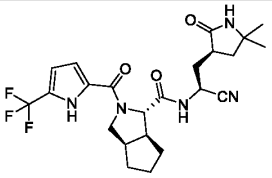
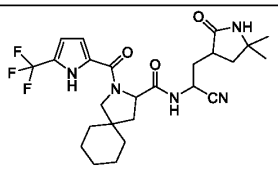
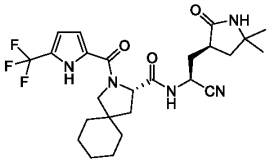
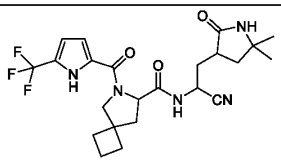
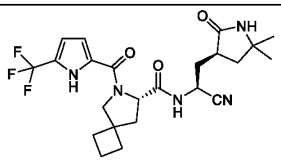
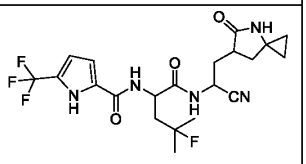
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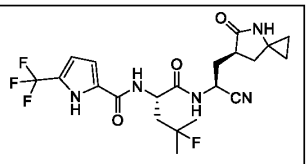
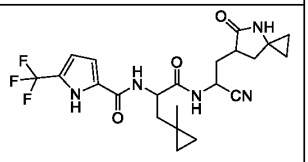
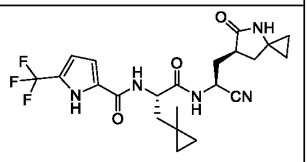
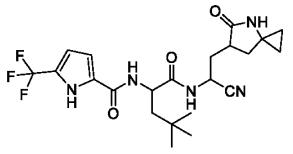
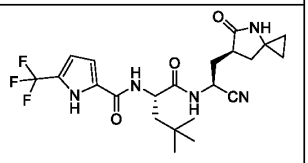
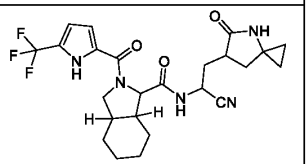
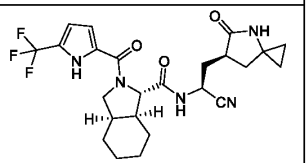
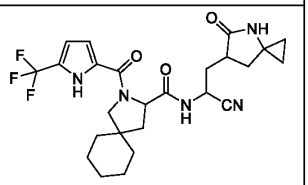
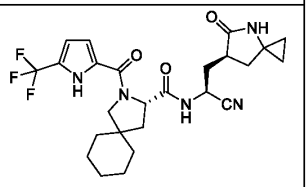
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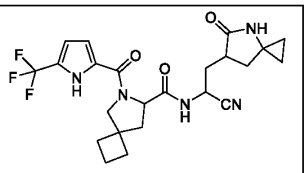
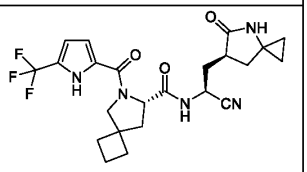
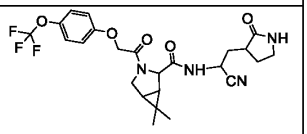
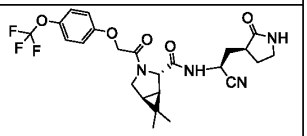
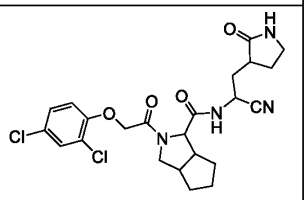
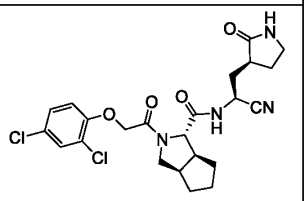
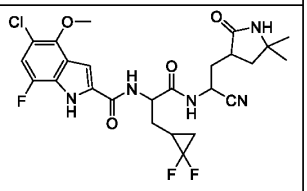
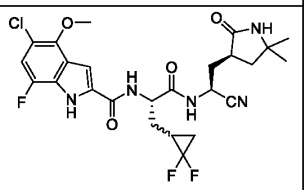
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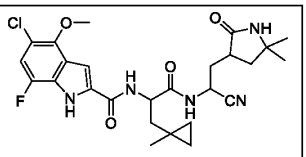
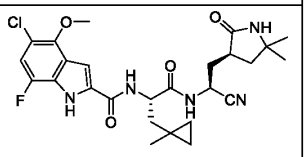
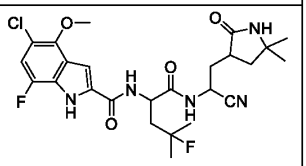
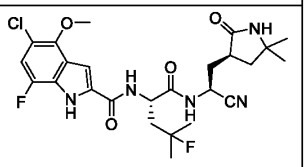
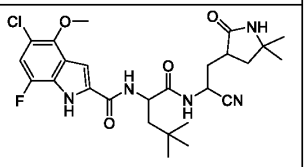
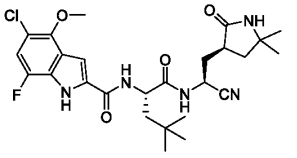
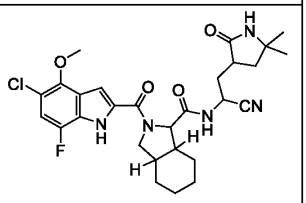
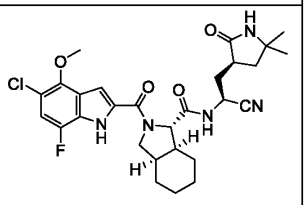
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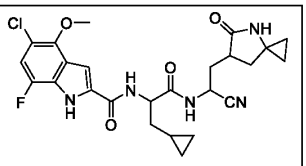
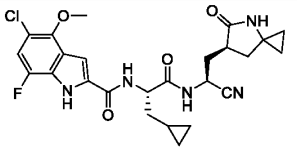
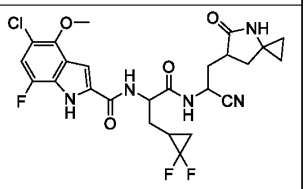
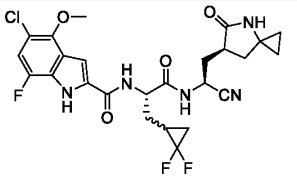
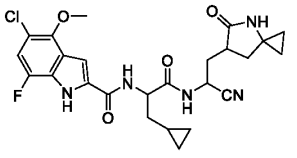
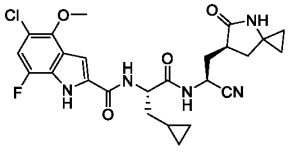
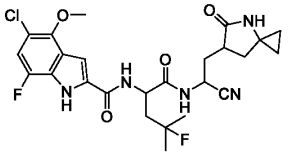
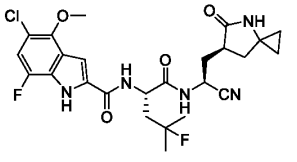
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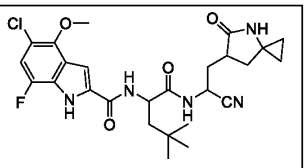
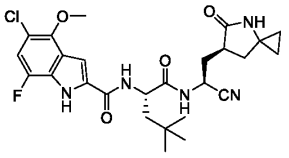
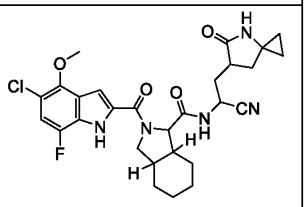
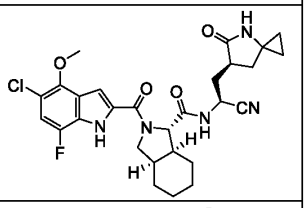
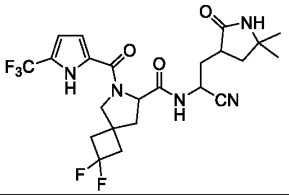
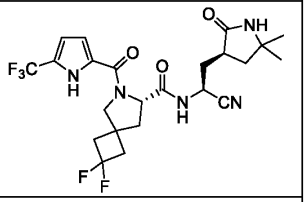
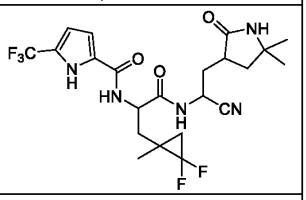
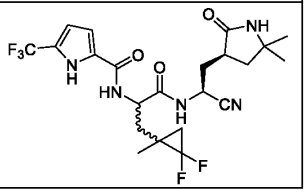
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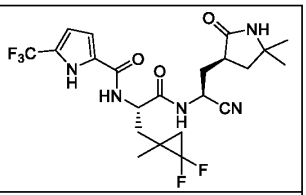
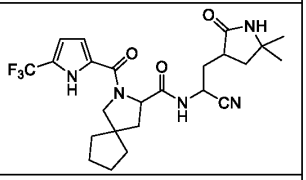
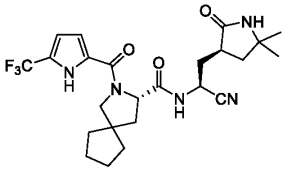
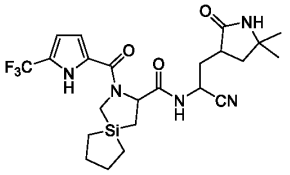
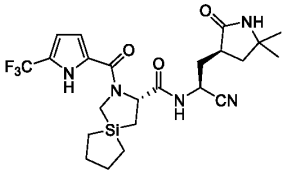
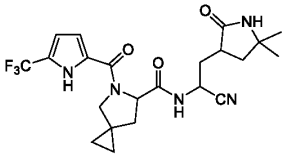
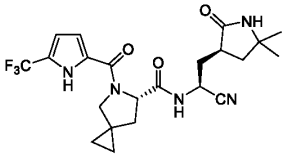
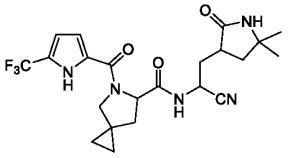
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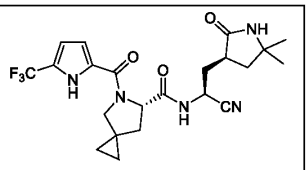
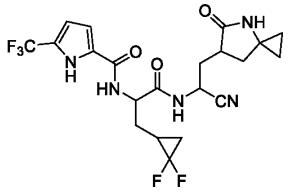
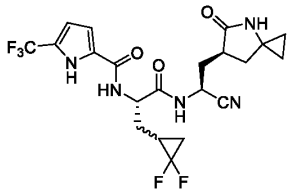
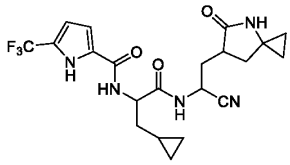
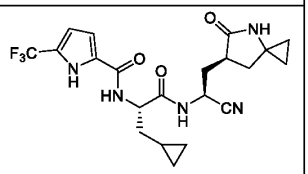
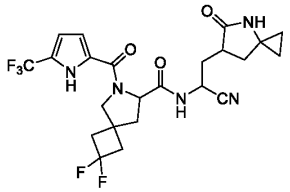
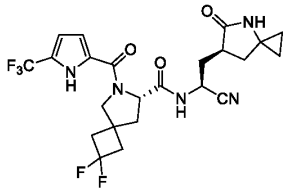
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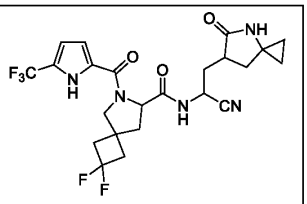
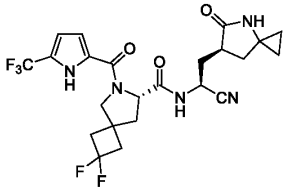
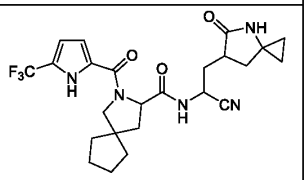
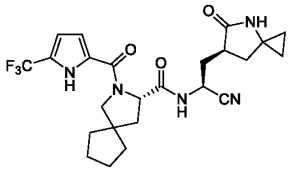
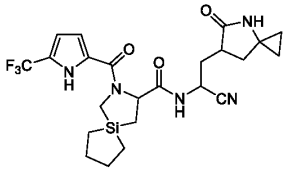
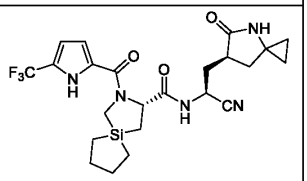
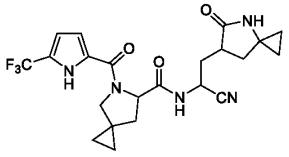
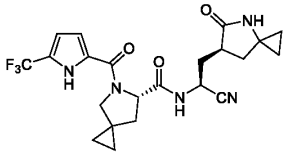
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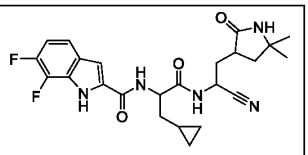
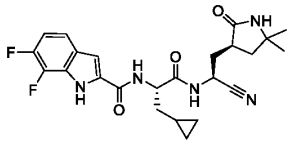
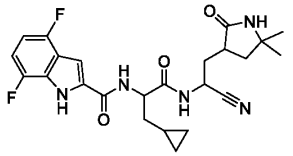
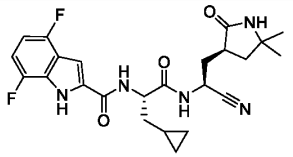
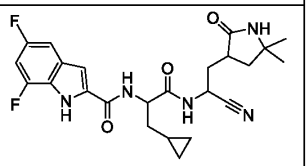
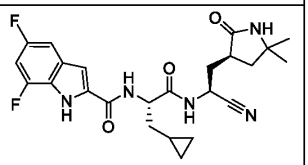
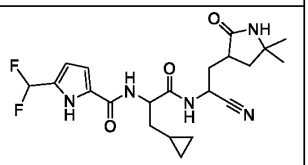
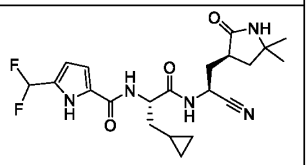
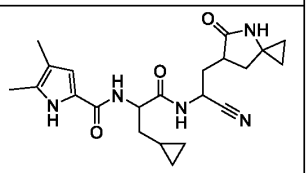
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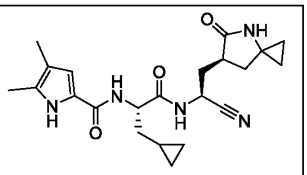
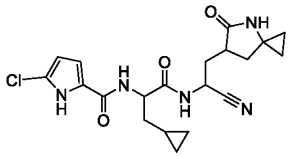
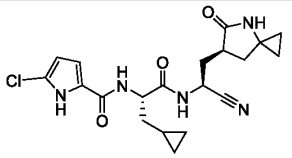
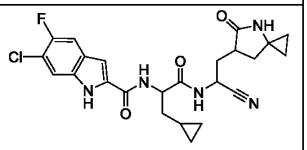
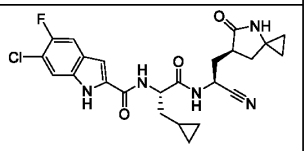
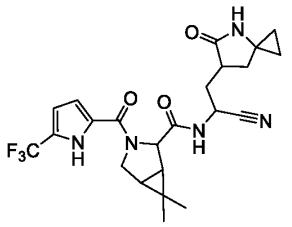
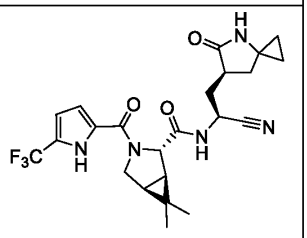
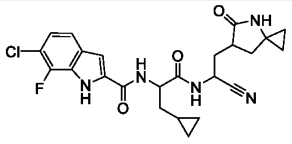
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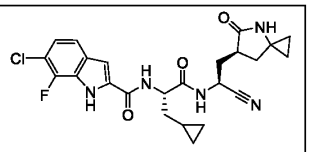
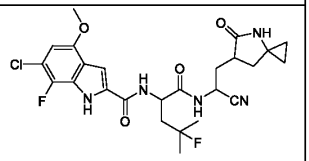
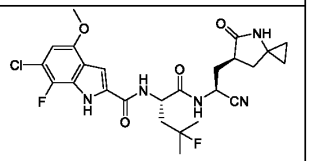
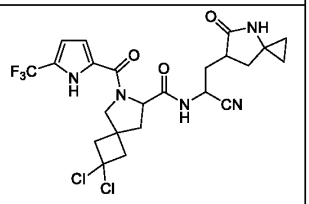
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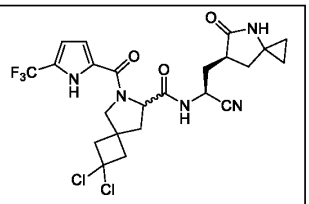
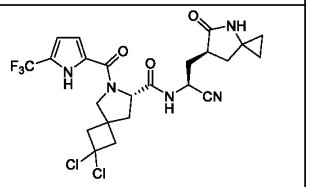
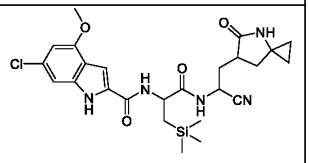
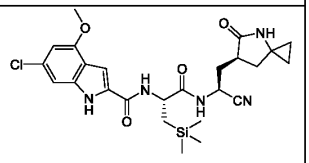
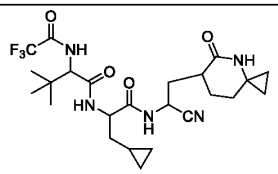
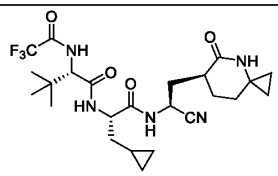
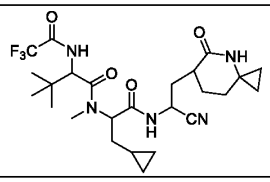
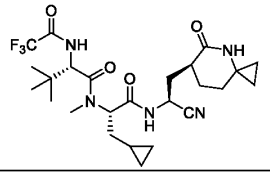
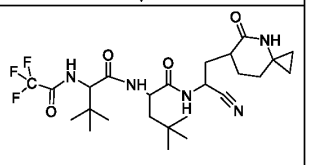
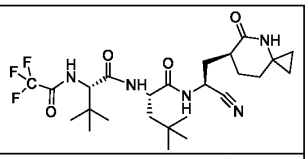
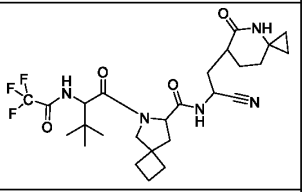
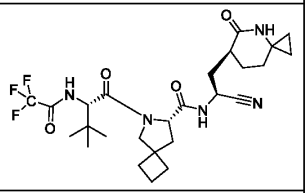
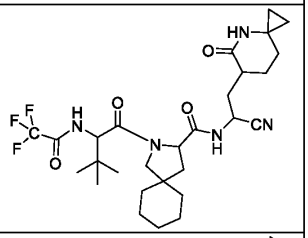
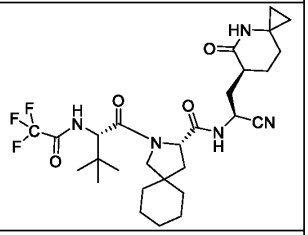
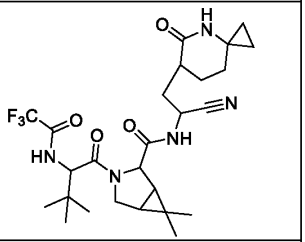
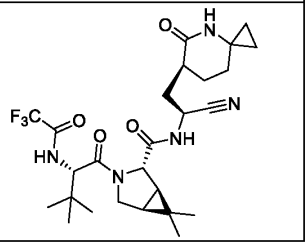
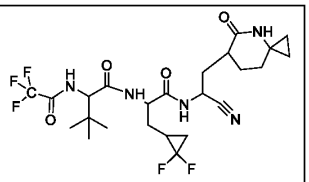
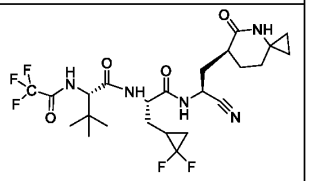
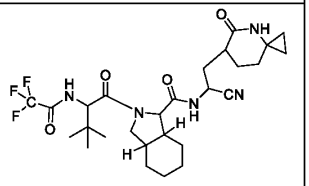
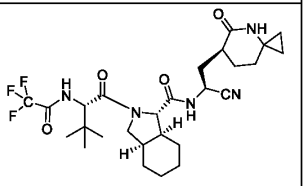
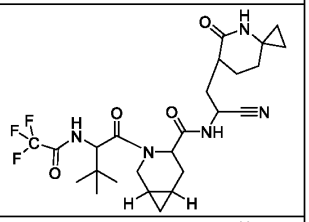
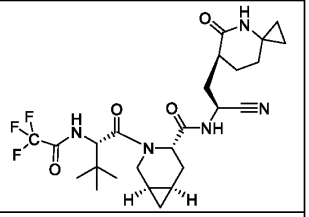
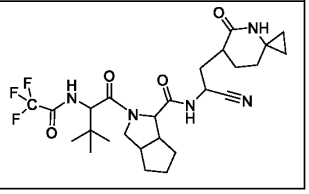
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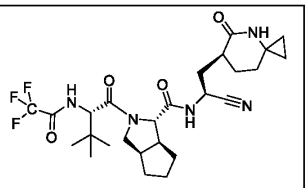
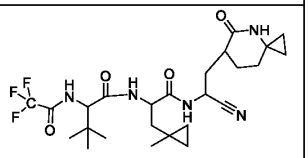
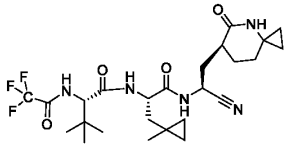
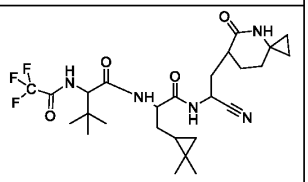
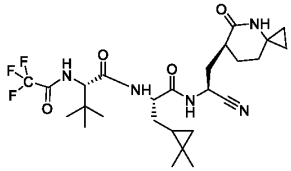
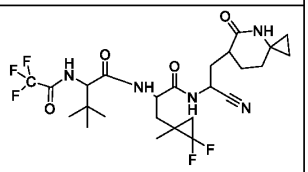
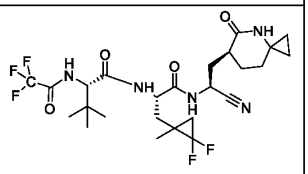
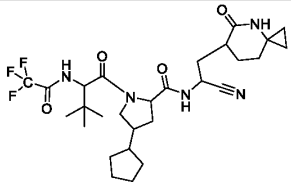
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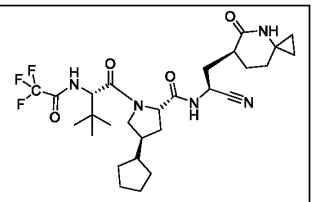
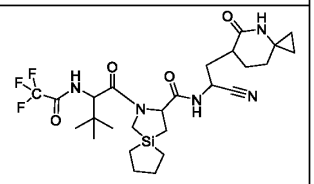
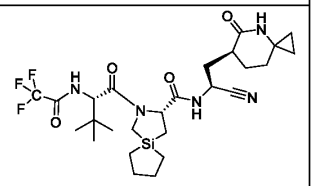
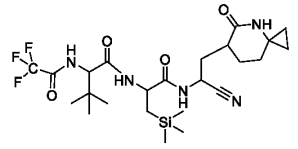
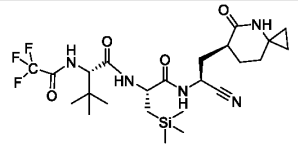
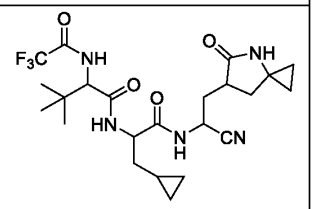
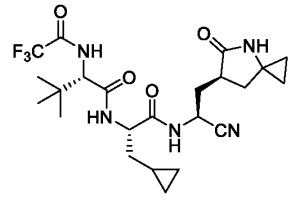
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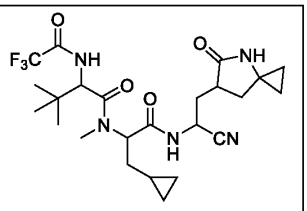
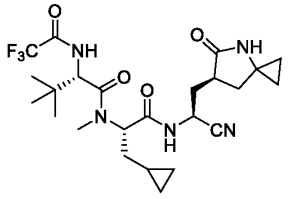
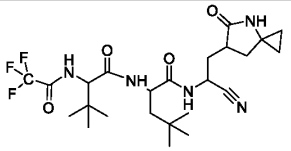
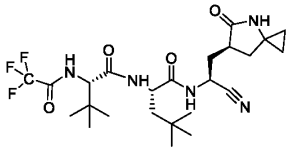
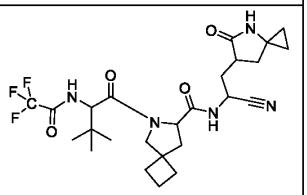
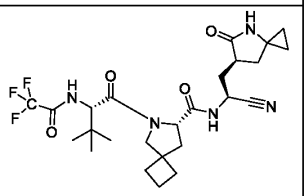
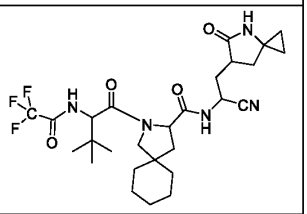
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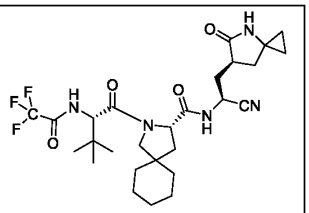
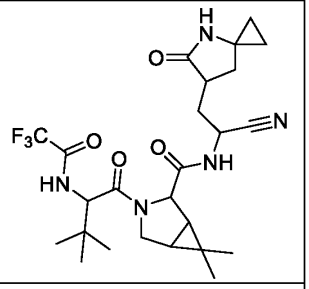
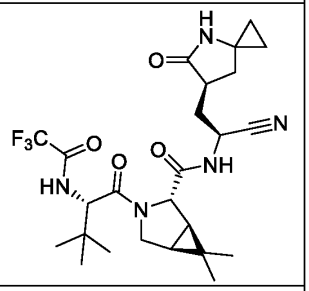
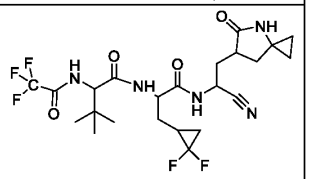
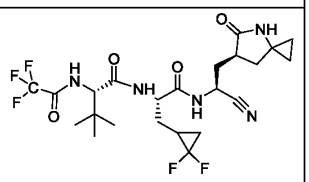
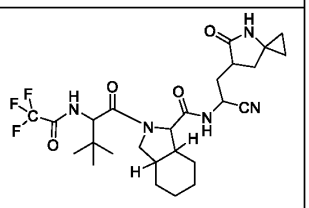
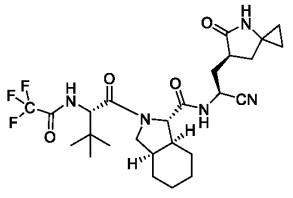
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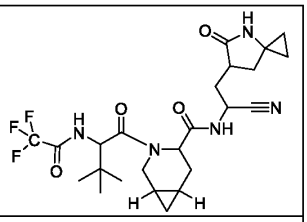
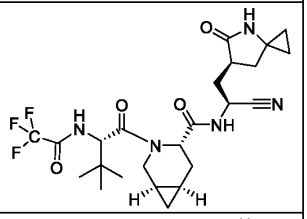
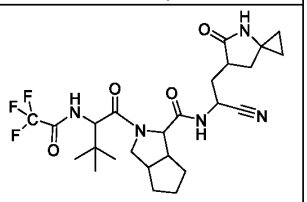
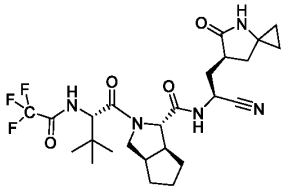
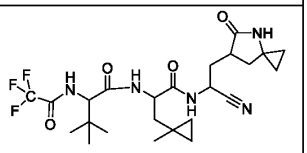
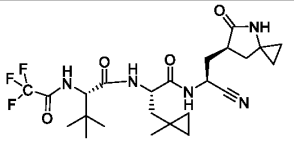
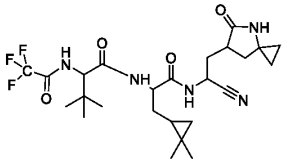
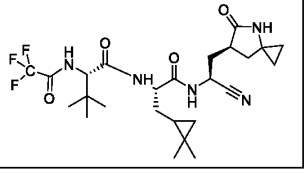
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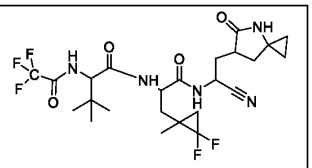
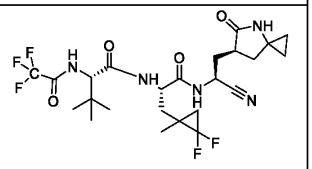
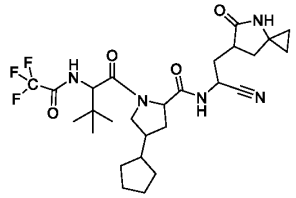
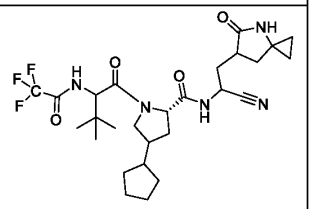
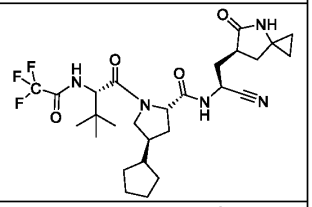
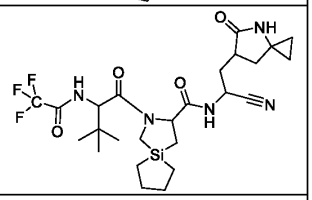
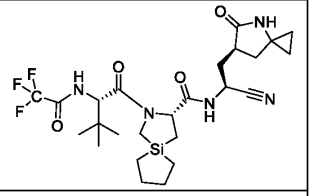
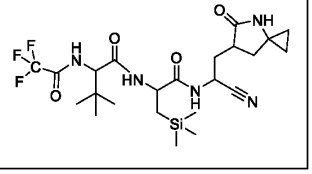
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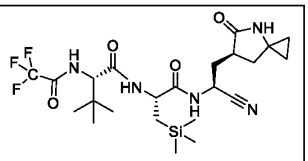
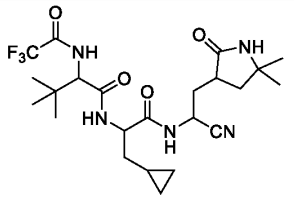
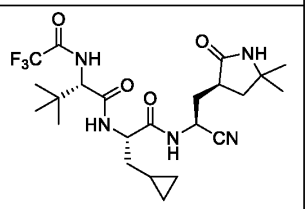
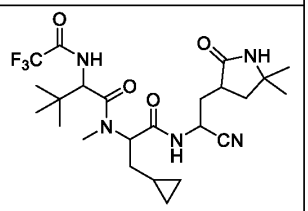
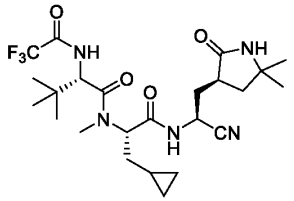
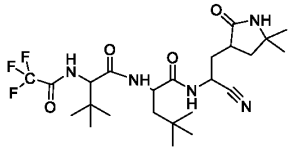
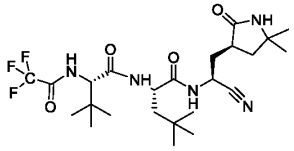
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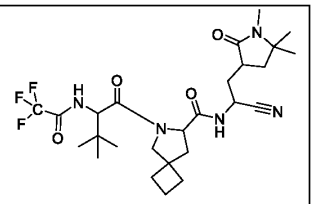
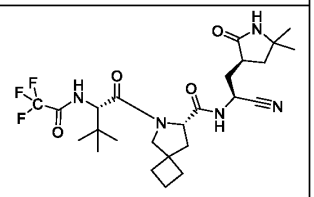
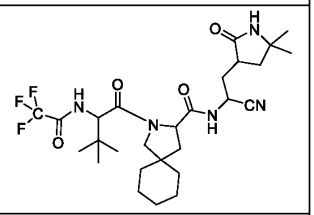
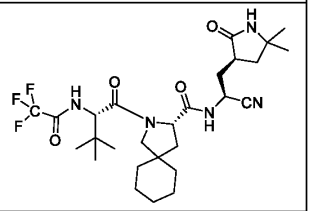
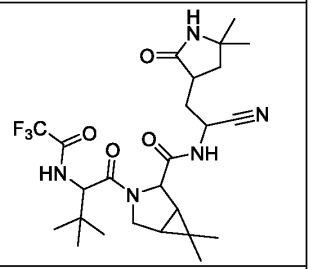
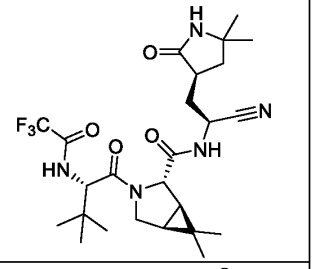
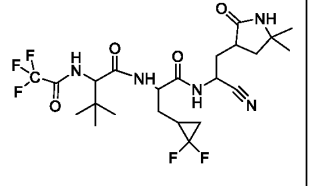
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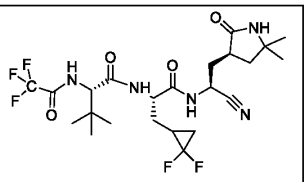
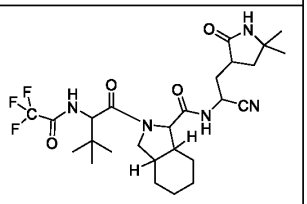
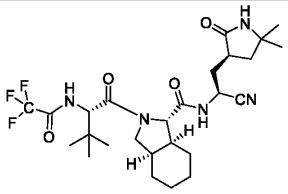
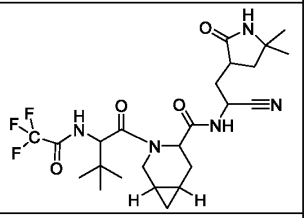
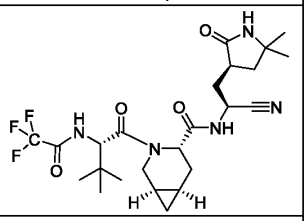
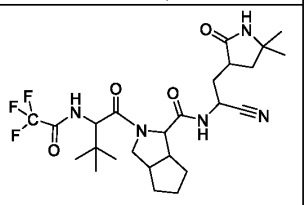
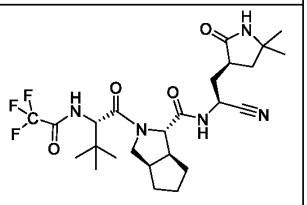
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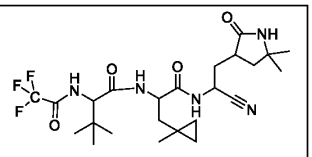
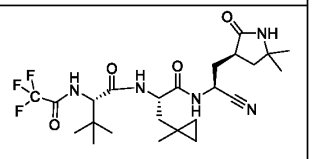
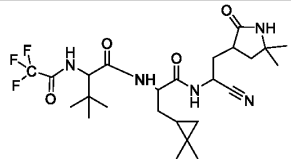
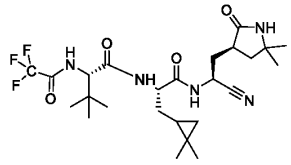
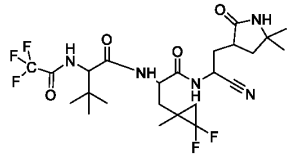
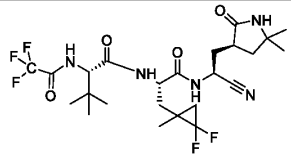
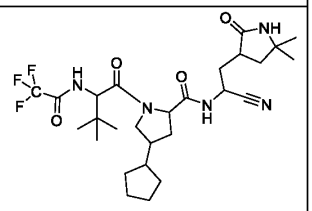
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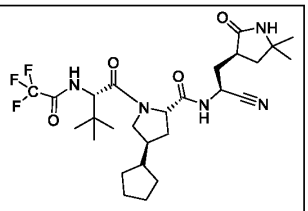
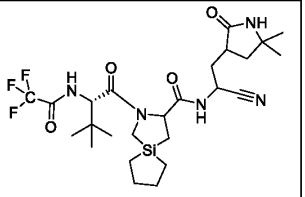
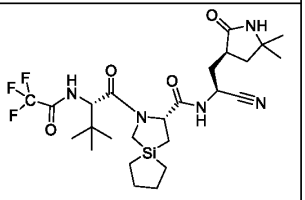
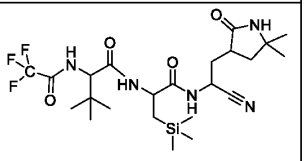
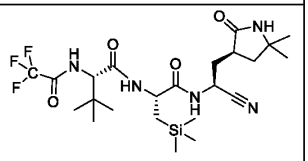
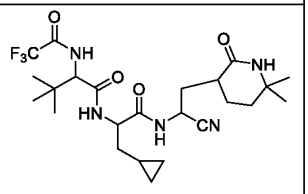
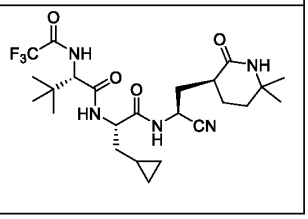
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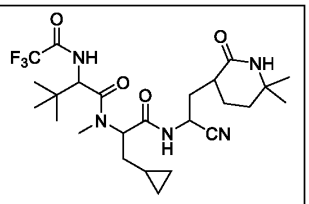
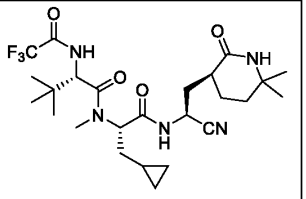
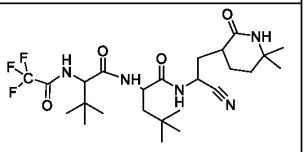
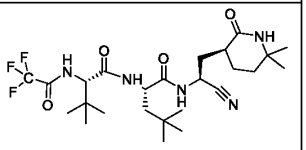
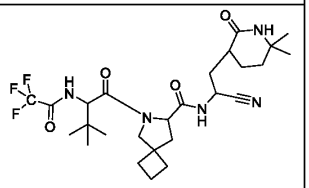
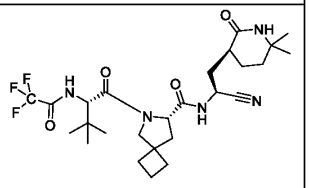
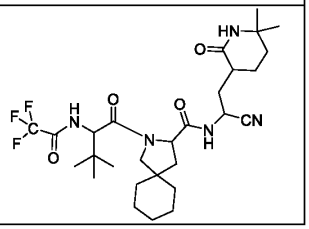
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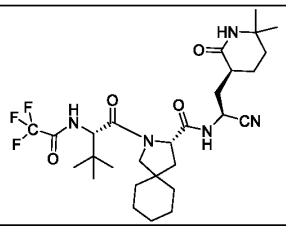
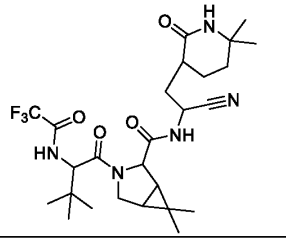
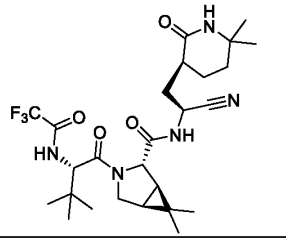
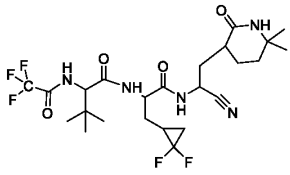
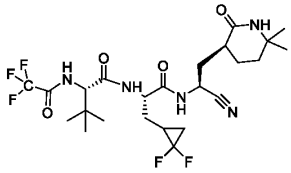
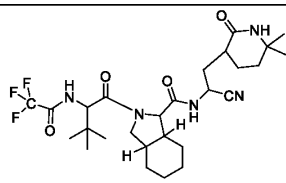
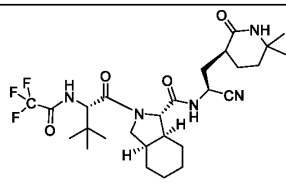
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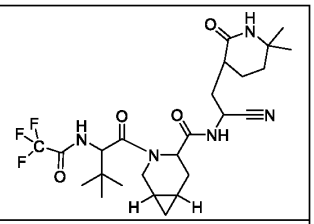
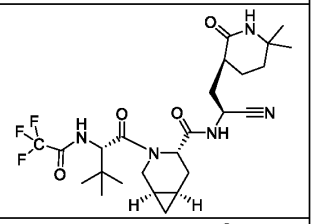
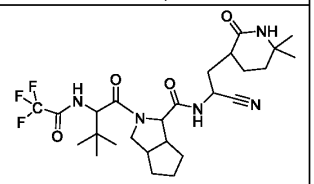
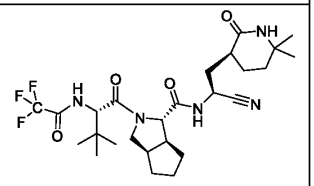
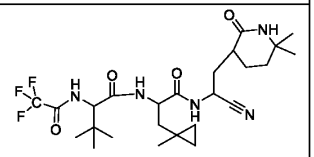
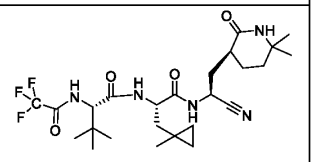
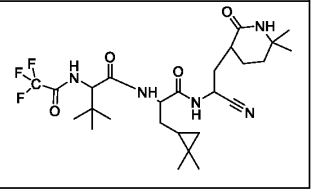
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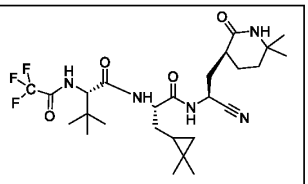
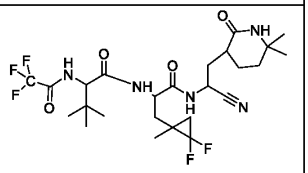
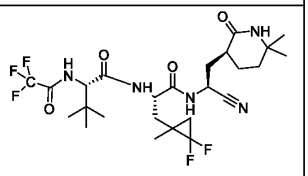
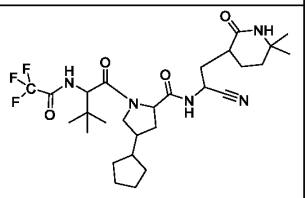
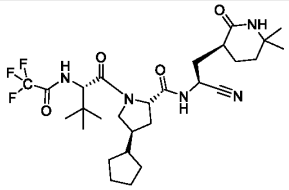
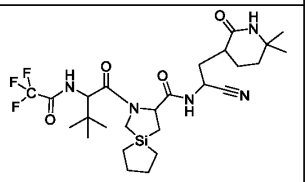
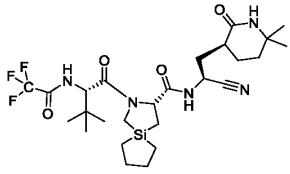
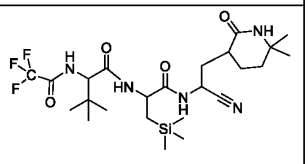
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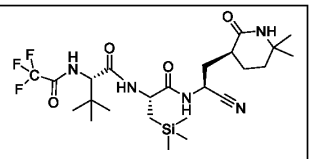
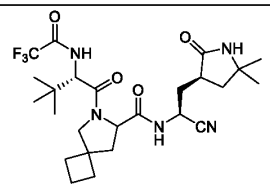
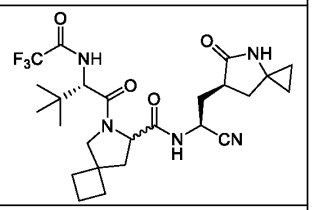
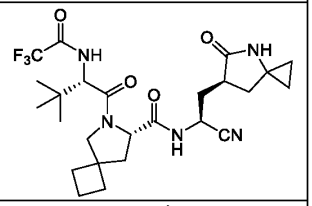
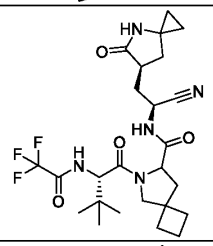
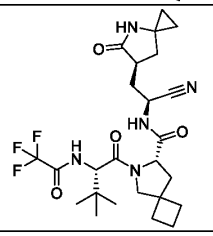
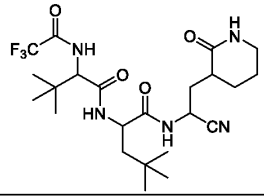
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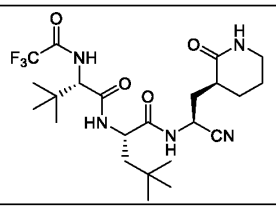
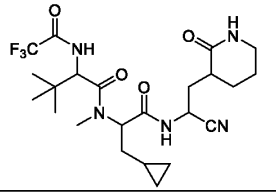
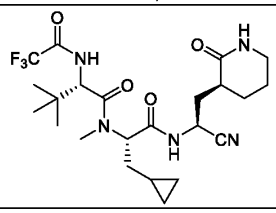
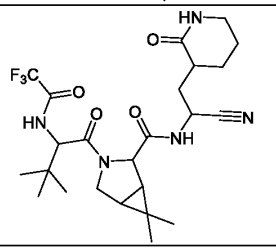
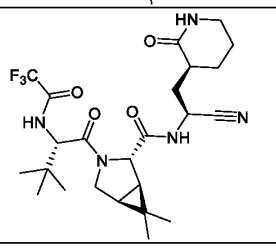
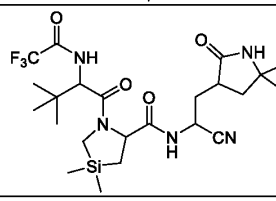
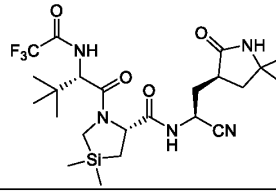
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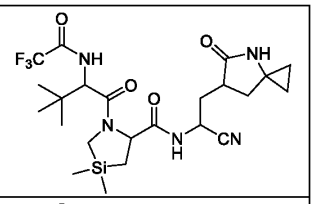
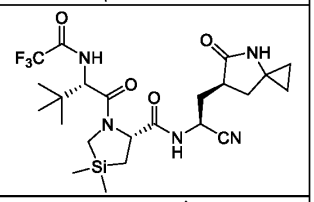
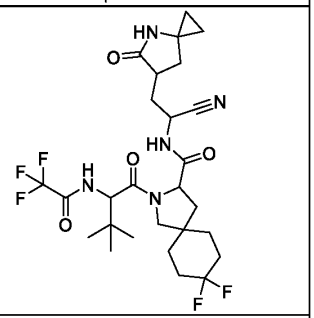
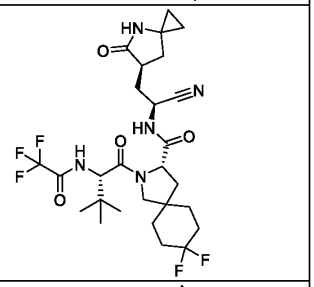
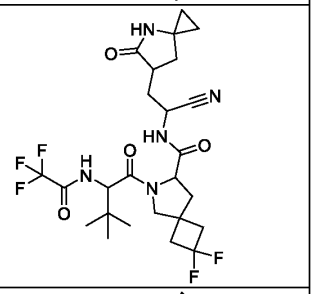
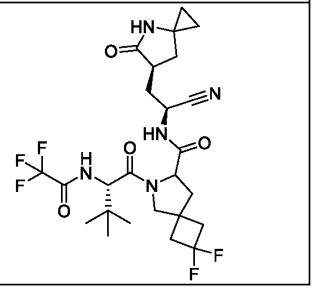
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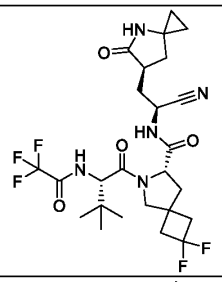
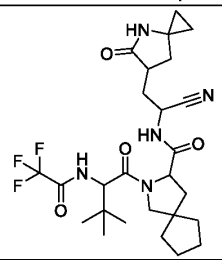
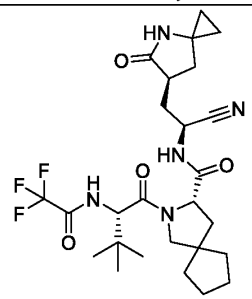
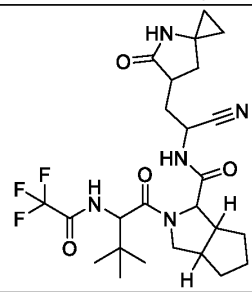
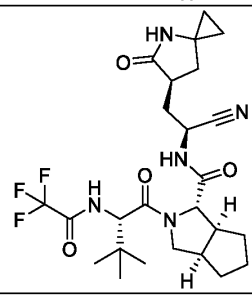
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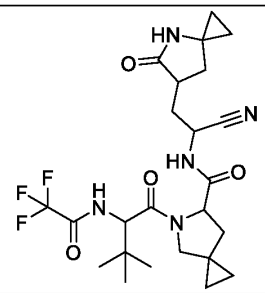
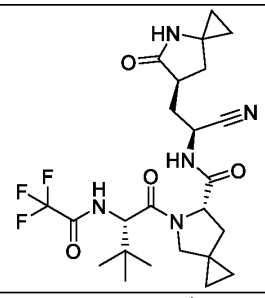
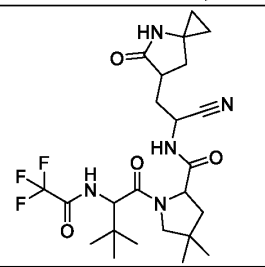
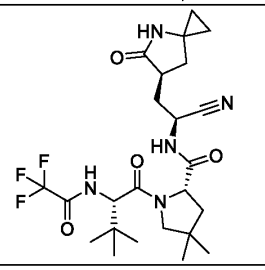
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II. Methods

[000127] Another aspect of the disclosure provides methods of treating patients suffering from a viral infection, e.g., a coronaviral infection. In particular, in certain embodiments, the disclosure provides a method of treating contemplated medical indications comprising administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A or IV-B.

[000128] In certain embodiments, the disclosure provides a method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds described herein. In some embodiments, the viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus (e.g., enterovirus 71 (EV71), an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus. In certain embodiments, the viral infection is a coronavirus infection. In some embodiments, the viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19). In embodiments, the viral infection is SARS-CoV-2.

[000129] In some embodiments, the viral infection is from a virus selected from the group consisting of calicivimses, MD145, murine norovirus, vesicular exanthema of swine virus, abbit hemorrhagic disease virus, porcine teschovirus, bovine coronavirus, feline infectious peritonitis virus, EV-68 virus, EV-71 virus, poliovirus, norovirus, human rhinovirus (HRV), hepatitis A virus (HAV) and foot-and-mouth disease virus (FMDV).

[000130] In embodiments, the viral infection is an arenavirus infection. In some embodiments, the arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus. In some embodiments, the viral infection is an influenza infection. In some embodiments, the influenza is influenza H1N1, H3N2 or H5N1.

[000131] Another aspect of the disclosure provides methods of treating patients suffering from a viral infection, e.g., a noroviral infection. In some embodiments, the disclosure provides a method of treating a viral infection from a norovirus in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds described herein.

[000132] Also provided herein, in certain embodiments, is a method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of a compound described herein to a patient suffering from the virus, and/or contacting an effective amount of a compound described herein with a virally infected cell. In some embodiments, the method further comprises administering another therapeutic. In some embodiments, the method further comprises administering an additional anti-viral therapeutic. In embodiments, the anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine. In some embodiments, the another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6-endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin,

ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine. In embodiments, the additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.

[000133] Contemplated patients include not only humans, but other animals such as companion animals (e.g. dogs, cats), domestic animals (e.g. cow, swine), and wild animals (e.g. monkeys, bats, snakes).

[000134] Accordingly, in one embodiment, described herein is a method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., a compound of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A or IV-B as described herein) or a pharmaceutically acceptable salt thereof.

[000135] Other contemplated methods of treatment include a method of treating or ameliorating a virus infection condition or co-morbidity, by administering an effective amount a compound disclosed herein to a subject in need thereof.

[000136] Exemplary co-morbidities include lung diseases, cardiac disorders, endocrine disorders, respiratory disorders, hepatic disorders, skeletal disorders, psychiatric disorders, metabolic disorders, and reproductive disorders.

[000137] In some embodiments, the viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus. In some embodiments, the viral infection is a coronavirus infection. In some embodiments, the viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19). In some embodiments, the viral infection is SARS-CoV-2. In some embodiments, the viral infection is an arenavirus infection. In some embodiments, the arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus. In some embodiments, the viral infection is an influenza infection. In some embodiments, the influenza is influenza H1N1, H3N2 or H5N1. In some embodiments, the viral infection is a respiratory viral infection. In some embodiments, the viral infection is an upper respiratory viral infection or a lower respiratory viral infection. In some embodiments, the method further comprises administering another therapeutic.

[000138] In certain embodiments, the virus is selected from the group consisting of a retrovirus (*e.g.*, human immunodeficiency virus (HIV), simian immunodeficiency virus (SIV), human T-cell lymphotropic virus (HTLV)-1, HTLV-2, HTLV-3, HTLV-4), Ebola virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, a herpes simplex virus (HSV) (*e.g.*, HSV-1, HSV-2, varicella zoster virus, cytomegalovirus), an adenovirus, an orthomyxovirus (*e.g.*, influenza virus A, influenza virus B, influenza virus C, influenza virus D, togavirus), a flavivirus (*e.g.*, dengue virus, Zika virus), West Nile virus, Rift Valley fever virus, an arenavirus, Crimean-Congo hemorrhagic fever virus, an echovirus, a rhinovirus, coxsackie virus, a coronavirus (*e.g.*, Severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), a respiratory syncytial virus, a mumps virus, a rotavirus, measles virus, rubella virus, a parvovirus (*e.g.*, an adeno-associated virus), a vaccinia virus, a variola virus, a molluscum virus, bovine leukemia virus, bovine diarrhea virus, a poliovirus, St. Louis encephalitis virus, Japanese encephalitis virus, a tick-borne encephalitis virus, Murray Valley virus, Powassan virus, Rocio virus, louping-ill virus, Banzi virus, Ilheus virus, Kokobera virus, Kunjin virus, Alfuy virus, a rabies virus, a polyomavirus (*e.g.*, JC virus, BK virus), an alphavirus, and a rubivirus (*e.g.*, rubella virus).

[000139] In certain embodiments, the disease or disorder is a viral infection, *e.g.*, a disease or disorder selected from the group consisting of acquired immune deficiency syndrome (AIDS), HTLV-1 associated myelopathy/tropical spastic paraparesis, Ebola virus disease, hepatitis A, hepatitis B, hepatitis C, herpes, herpes zoster, acute varicella, mononucleosis, respiratory infections, pneumonia, influenza, dengue fever, encephalitis (*e.g.*, Japanese encephalitis, St. Louis encephalitis, or tick-borne encephalitis such as Powassan encephalitis), West Nile fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, Kyasanur Forest disease, Yellow fever, Zika fever, aseptic meningitis, myocarditis, common cold, lung infections, molloscum contagiosum, enzootic bovine leucosis, coronavirus disease 2019 (COVID-19), mumps, gastroenteritis, measles, rubella, slapped-cheek disease, smallpox, warts (*e.g.*, genital warts), molluscum contagiosum, polio, rabies, and pityriasis rosea.

[000140] In some embodiments, the virus is an RNA virus (having a genome that is composed of RNA). RNA viruses may be single-stranded RNA (ssRNA) or double-stranded RNA (dsRNA). RNA viruses have high mutation rates compared to DNA viruses, as RNA polymerase lacks proofreading capability (see, e.g., Steinhauer DA, Holland JJ (1987). "Rapid evolution of RNA viruses". Annu. Rev. Microbiol. 41: 409–33). In some embodiments, the RNA virus is a positive-strand RNA virus (e.g., a SARS-CoV virus, polio virus, Coxsackie virus, Enterovirus, Human rhinovirus, Foot/Mouth disease virus, encephalomyocarditis virus, Dengue virus, Zika virus, Hepatitis C virus, or New Castle Disease virus).

[000141] RNA viruses are classified by the type of genome (double-stranded, negative (-), or positive (+) single-stranded). Double-stranded RNA viruses contain a number of

different RNA molecules, each coding for one or more viral proteins. Positive-sense ssRNA viruses utilize their genome directly as mRNA; ribosomes within the host cell translate mRNA into a single protein that is then modified to form the various proteins needed for viral replication. One such protein is RNA-dependent RNA polymerase (RNA replicase), which copies the viral RNA in order to form a double-stranded, replicative form. Negative-sense ssRNA viruses have their genome copied by an RNA replicase enzyme to produce positive-sense RNA for replication. Therefore, the virus comprises an RNA replicase enzyme. The resultant positive-sense RNA then acts as viral mRNA and is translated by the host ribosomes. In some embodiments, the virus is a dsRNA virus. In some embodiments, the virus is a negative ssRNA virus. In some embodiments, the virus is a positive ssRNA virus. In some embodiments, the positive ssRNA virus is a coronavirus.

[000142] SARS-CoV2, also sometimes referred to as the novel coronavirus of 2019 or 2019-nCoV, is a positive-sense single-stranded RNA virus. SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. The N protein holds the RNA genome together; the S, E, and M proteins form the viral envelope. Spike allows the virus to attach to the membrane of a host cell, such as the ACE2 receptor in human cells (Kruse R.L. (2020), Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China (version 2). *F1000Research*, 9:72). SARS-CoV2 is the highly contagious, causative viral agent of coronavirus disease 2019 (COVID19), a global pandemic.

[000143] In some embodiments, the virus is a DNA virus (having a genome that is composed of DNA). Exemplary DNA viruses include, without limitation, parvoviruses (*e.g.*, adeno-associated viruses), adenoviruses, asfarviruses, herpesviruses (*e.g.*, herpes simplex virus 1 and 2 (HSV-1 and HSV-2), Epstein-Barr virus (EBV), cytomegalovirus (CMV)), papillomaviruses (*e.g.*, HPV), polyomaviruses (*e.g.*, simian vacuolating virus 40 (SV40)), and poxviruses (*e.g.*, vaccinia virus, cowpox virus, smallpox virus, fowlpox virus, sheeppox virus, myxoma virus). Exemplary RNA viruses include, without limitation, bunyaviruses (*e.g.*, hantavirus), coronaviruses, flaviviruses (*e.g.*, yellow fever virus, west Nile virus, dengue virus), hepatitis viruses (*e.g.*, hepatitis A virus, hepatitis C virus, hepatitis E virus), influenza viruses (*e.g.*, influenza virus type A, influenza virus

type B, influenza virus type C), measles virus, mumps virus, calicivirus, noroviruses (*e.g.*, Norwalk virus), poliovirus, respiratory syncytial virus (RSV), retroviruses (*e.g.*, human immunodeficiency virus-1 (HIV-1)) and toroviruses.

[000144] The methods described herein may inhibit viral replication transmission, replication, assembly, or release, or minimize expression of viral proteins. In one embodiment, described herein is a method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, to a patient suffering from the virus, and/or contacting an effective amount of a compound described herein or a pharmaceutically acceptable salt thereof, with a virally infected cell.

[000145] Also described herein is a method of treating a respiratory disorder in a subject in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., a compound of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A, or IV-B, etc. described herein) or a pharmaceutically acceptable salt thereof. In certain embodiments, the respiratory disorder is selected from the group consisting of chronic obstructive pulmonary disease (COPD), asthma, fibrosis, chronic asthma, acute asthma, lung disease secondary to environmental exposures, acute lung infection, chronic lung infection, a1 antitrypsin disease, cystic fibrosis and an autoimmune disease. In some embodiments, the respiratory disorder is associated with a heart attack.

[000146] Also described herein is a method of treating a disorder associated with cathepsin (e.g. Cathepsin K) in a subject in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., a compound of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A, or IV-B, etc. described herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the disorder is a cathepsin dependent condition or disease. In embodiments, the disorder is selected from the group consisting of breast cancer, pycnodysostosis, glioblastoma, osteosclerosis, osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis,

periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma.

[000147] Compounds described herein, e.g., a compound of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A, IV-B etc. as defined herein, can be administered in combination with one or more additional therapeutic agents to treat a disorder described herein, such as an infection by a pathogen described herein, e.g., a virus, fungus, or protozoan. For clarity, contemplated herein are both a fixed composition comprising a disclosed compound and another therapeutic agent such as disclosed herein, and methods of administering, separately a disclosed compound and a disclosed therapeutic. For example, provided in the present disclosure is a pharmaceutical composition comprising a compound described herein, e.g., a compound of Formula I as defined herein, one or more additional therapeutic agents, and a pharmaceutically acceptable excipient. In some embodiments, a compound of Formula I as defined herein and one additional therapeutic agent is administered. In some embodiments, a disclosed compound as defined herein and two additional therapeutic agents are administered. In some embodiments, a disclosed compound as defined herein and three additional therapeutic agents are administered. Combination therapy can be achieved by administering two or more therapeutic agents, each of which is formulated and administered separately. For example, a compound of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A, IV-B, etc. as defined herein and an additional therapeutic agent can be formulated and administered separately. Combination therapy can also be achieved by administering two or more therapeutic agents in a single formulation, for example a pharmaceutical composition comprising a compound of Formula I as one therapeutic agent and one or more additional therapeutic agents such as an antibiotic, a viral protease inhibitor, or an anti-viral nucleoside anti-metabolite. For example, a compound of Formula I as defined herein and an additional therapeutic agent can be administered in a single formulation. Other combinations are also encompassed by combination therapy. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or

weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[000148] Combination therapy can also include two or more administrations of one or more of the agents used in the combination using different sequencing of the component agents. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

[000149] In some embodiments, the one or more additional therapeutic agents that may be administered in combination with a compound provided herein can be an antibiotic, a viral protease inhibitor, an anti-viral anti-metabolite, a lysosomotropic agent, a M2 proton channel blocker, a polymerase inhibitor (e.g., EIDD-2801, which is also known as MOLNUPIRAVIR), aneuraminidase inhibitor, a reverse transcriptase inhibitor, a viral entry inhibitor, an integrase inhibitor, interferons (e.g., types I, II, and III), or a nucleoside analogue. In some embodiments, the one or more additional therapeutic agents that may be administered in combination wiht a compounds provided herein can be a steroid (e.g., corticosteroids, such as bethamethasone, prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone; mineralcorticoid such as fludrocortisone; glucocorticoids, such as hydrocortisone, cortisone, ethamethasoneb, prednisone, prednisolone, triamcinolone, dexamethasone; vitamin D such as dihydrotachysterol; androgens such as apoptone, oxandrolone, oxabolone, testosterone, nandrolone (also known as anabolic steroids), oestrogens such as diethylstilbestrol, progestins such as danazol, norethindrone, medroxyprogesterone acetate, 17-Hydroxyprogesterone caproate; and progestins such as mifepristone and gestrinone) or an immunomodulator (e.g., 6Mercaptopurine, 6MP, Alferon N, anakinra, Arcalyst, Avonex, AVOSTARTGRIP, Bafiertam, Berinert, Betaseron, BG-12, C1 esterase inhibitor recombinant, C1 inhibitor human, Cinryze, Copaxone, dimethyl fumarate, diroximel fumarate, ecallantide, emapalumab, emapalumab-lzsg, Extavia, fingolimod, Firazyr,

Gamifant, Gilenya, glatiramer, Glatopa, Haegarda, icatibant, Infergen, interferon alfa n3, interferon alfacon 1, interferon beta 1a, interferon beta 1b, Kalbitor, Kineret, mercaptopurine, monomethyl fumarate, peginterferon beta-1a, Plegridy, Purinethol, Purixan, Rebif, Rebif Rebidose, remestemcel-L, rilonacept, ropeginterferon alfa 2b, Ruconest, Ryoncil, siltuximab, sutimlimab, Sylvant, Tecfidera, and Vumerity). In some embodiments, the one or more additional therapeutic agent is Cathepsin L. In some embodiments, the one or more additional therapeutic agent is dehydrodidemnin B (also known as Plitidepsin or APLIDIN) or Zotatifin (eFT226).

[000150] In some embodiments, methods described herein further comprise administering an additional anti-viral therapeutic. In some embodiments, the anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine. In some embodiments, the another therapeutic is selected from the group consisting of protease inhibitors (e.g., nafamostat, camostat, gabexate, epsilon-aminocapronic acid and aprotinin), fusion inhibitors (e.g., BMY-27709, CL 61917, and CL 62554), M2 proton channel blockers (e.g., amantadine and rimantadine), polymerase inhibitors (e.g., 2-deoxy-2'fluoroguanosides (2'-fluoroGuo), 6- endonuclease inhibitors (e.g., L-735,822 and flutamide) neuraminidase inhibitors (e.g., zanamivir (Relenza), oseltamivir, peramivir and ABT-675 (A-315675), reverse transcriptase inhibitor (e.g., abacavir, adefovir, delavirdine, didanosine, efavirenz, emtricitabine, lamivudine, nevirapine, stavudine, tenofovir, tenofovir disoproxil, and zalcitabine), acyclovir, acyclovir, protease inhibitors (e.g., amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors

(e.g., enfuvirtide and maraviroc), entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor (e.g., raltegravir), interferons (e.g., types I, II, and III), lopinavir, loviride, moroxydine, nexavir, nucleoside analogues (e.g., aciclovir), penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine. In some embodiments, the additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine. In some embodiments, the another therapeutic is selected from the group consisting of quinine (optionally in combination with clindamycin), chloroquine, amodiaquine, artemisinin and its derivatives (e.g., artemether, artesunate, dihydroartemisinin, arteether), doxycycline, pyrimethamine, mefloquine, halofantrine, hydroxychloroquine, eflornithine, nitazoxanide, ornidazole, paromomycin, pentamidine, primaquine, pyrimethamine, proguanil (optionally in combination with atovaquone), a sulfonamide (e.g., sulfadoxine, sulfamethoxypyridazine), tafenoquine, tinidazole and a PPT1 inhibitor (including Lys05 and DC661). In some embodiments, the another therapeutic is an antibiotic. In some embodiments, the antibiotic is a penicillin antibiotic, a quinolone antibiotic, a tetracycline antibiotic, a macrolide antibiotic, a lincosamide antibiotic, a cephalosporin antibiotic, or an RNA synthetase inhibitor. In some embodiments, the antibiotic is selected from the group consisting of azithromycin, vancomycin, metronidazole,

gentamicin, colistin, fidaxomicin, telavancin, oritavancin, dalbavancin, daptomycin, cephalexin, cefuroxime, cefadroxil, cefazolin, cephalothin, cefaclor, cefamandole, cefoxitin, cefprozil, ceftobiprole, cipro, Levaquin, floxin, tequin, avelox, norflox, tetracycline, minocycline, oxytetracycline, doxycycline, amoxicillin, ampicillin, penicillin V, dicloxacillin, carbenicillin, methicillin, ertapenem, doripenem, imipenem/cilastatin, meropenem, amikacin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefoxotin, and streptomycin. In some embodiments, the antibiotic is azithromycin.

[000151] In some embodiments, the one or more additional therapeutic agents that may be administered in combination with a compound provided herein can be selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.

[000152] In some embodiments, the compounds described herein (e.g. of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A, IV-B, etc.) and pharmaceutically acceptable salts thereof may be used in combination with one or more other agents which may be useful in the prevention or treatment of respiratory disease, inflammatory disease, autoimmune disease, for example; anti-histamines, corticosteroids, (e.g., fluticasone propionate, fluticasone furoate, beclomethasone dipropionate, budesonide, ciclesonide, mometasone furoate, triamcinolone, flunisolide), NSAIDs, leukotriene modulators (e.g., montelukast, zafirlukast, pranlukast), tryptase inhibitors, IKK2 inhibitors, p38 inhibitors, Syk

inhibitors, protease inhibitors such as elastase inhibitors, integrin antagonists (e.g., beta-2 integrin antagonists), adenosine A2a agonists, mediator release inhibitors such as sodium chromoglycate, 5-lipoxygenase inhibitors (zyflo), DP1 antagonists, DP2 antagonists, PI3K delta inhibitors, ITK inhibitors, LP (lysophosphatidic) inhibitors or FLAP (5-lipoxygenase activating protein) inhibitors (e.g., sodium 3-(3-(tert-butylthio)-1 -(4-(6-ethoxypyridin-3-yl)benzyl)-5-((5-ethylpyridin-2-yl)methoxy)-1 H-indol-2-yl)-2,2-dimethylpropanoate), bronchodilators (e.g..muscarinic antagonists, beta-2 agonists), methotrexate, and similar agents; monoclonal antibody therapy such as anti-lgE, anti-TNF, anti-IL-5, anti-IL-6, anti-IL-12, anti-IL-1 and similar agents; cytokine receptor therapies e.g. etanercept and similar agents; antigen non-specific immunotherapies (e.g. interferon or other cytokines/chemokines, chemokine receptor modulators such as CCR3, CCR4 or CXCR2 antagonists, other cytokine/chemokine agonists or antagonists, TLR agonists and similar agents), suitable anti-infective agents including antibiotic agents, antifungal agents, anthelmintic agents, antimalarial agents, antiprotozoal agents and antituberculosis agents.

[000153] In some embodiments, the additional therapeutic agents can be kinase inhibitors including but not limited to erlotinib, gefitinib, neratinib, afatinib, osimertinib, lapatanib, crizotinib, brigatinib, ceritinib, alectinib, lorlatinib, everolimus, temsirolimus, abemaciclib, LEE011, palbociclib, cabozantinib, sunitinib, pazopanib, sorafenib, regorafenib, axitinib, dasatinib, imatinib, nilotinib, ponatinib, idelalisib, ibrutinib, Loxo 292, larotrectinib, and quizartinib.

[000154] In some embodiments, the additional therapeutic agents can be therapeutic anti-viral vaccines.

[000155] In some embodiments, the additional therapeutic agents can be immunomodulatory agents including but not limited to anti-PD-1or anti-PDL-1 therapeutics including pembrolizumab, nivolumab, atezolizumab, durvalumab, BMS-936559, or avelumab, anti-TIM3 (anti-HAVcr2) therapeutics including but not limited to TSR-022 or MBG453, anti-LAG3 therapeutics including but not limited to relatlimab, LAG525, or TSR-033, anti-4-1BB (anti-CD37, anti-TNFRSF9), CD40 agonist therapeutics including but not limited to SGN-40, CP-870,893 or RO7009789, anti-CD47 therapeutics including but not limited to Hu5F9-G4, anti-CD20 therapeutics, anti-CD38

therapeutics, STING agonists including but not limited to ADU-S100, MK-1454, ASA404, or amidobenzimidazoles, anthracyclines including but not limited to doxorubicin or mitoxanthrone, hypomethylating agents including but not limited to azacytidine or decitabine, other immunomodulatory therapeutics including but not limited to epidermal growth factor inhibitors, statins, metformin, angiotensin receptor blockers, thalidomide, lenalidomide, pomalidomide, prednisone, or dexamethasone. In some embodiments, the additional therapeutic agent is a p2-adrenoreceptor agonist including, but not limited to, vilanterol, salmeterol, salbutamol.formoterol, salmefamol, fenoterol carmoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerbuterol, reproterol, bambuterol, indacaterol, terbutaline and salts thereof, for example the xinafoate (1 - hydroxy-2- naphthalenecarboxylate) salt of salmeterol, the sulphate salt of salbutamol or the fumarate salt of formoterol. In some embodiments, the additional therapeutic agent is an anticholinergic agent, including, but not limited to, umeclidinium (for example, as the bromide), ipratropium (for example, as the bromide), oxitropium (for example, as the bromide) and tiotropium (for example, as the bromide).

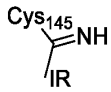
[000156] In particular, in certain embodiments, the disclosure provides a method of treating the above medical indications comprising administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a disclosed compound.

[000157] The term "boosting amount" or "boosting dose" is the amount of a compound needed to improve the pharmacokinetics of a second compound (or increase availability or exposure). The boosting amount or boosting dose may improve the pharmacokinetics (or increase availability or exposure) of the second compound to a level to therapeutic levels in a subject.

[000158] In one embodiment, the disclosure provides for a disclosed compound to be administered together with an antiviral therapeutic such as disclosed herein, and e.g., thereby boosting the dose of the anti-viral therapeutic or therapeutics. Such a boost combination may be used, e.g., as prophylactic or therapeutic treatment of a viral infection in a subject in need thereof. In one embodiment, the protease inhibitor is a compound described herein (e.g. of Formula II, II-A, II-B, II-C, II-D-A, II-D-B, II-E-A, II-E-B, II-F, II-G, II-H-A, II-H-B, II-E, II-I, IV-A, IV-B, etc.).

III. Reversible or Irreversible Conjugates

[000159] In certain embodiments, disclosed herein are conjugates represented by Formula III:



Formula III,

[000160] wherein Cys_{145} is cysteine at position 145 or equivalent active site cysteine on a CL or 3CL protease; IR is a viral protease inhibitor; and wherein the compound that forms the conjugate comprises a -CN warhead.

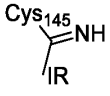
[000161] For example, disclosed herein is an engineered CL or 3CL viral protease, wherein:

the cysteine at position 145 of the CL or 3CL protease; has a non-naturally occurring covalent modification resulting from a reaction between an exogenous nitrile modifier having a nitrile function and the cysteine at position 145 of the CL or 3CL protease, and

wherein the sulfur atom at the cysteine residue and the nitrile of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein the engineered SARS- protease does not retain the protease activity of an unmodified CL or 2CL protease.

[000162] In some embodiments, the engineered viral protease substantially prevents viral replication of SARS-COV2. In some embodiments, the CL or 3CL protease is represented by SEQ ID NO: 1. In other embodiments, the enzymatic inhibition IC_{50} of the exogenous nitrile modifier for SEQ ID NO: 1 is less than 20 micromolar.

[000163] In some embodiments, the thioimidate adduct resulting from the in vivo reaction between the exogenous nitrile modifier and the cysteine at position 145 of SEQ ID NO: 1 is represented by:



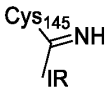
wherein

IR is the exogenous nitrile modifier after undergoing the reaction.

[000164] For example, disclosed herein is an engineered 3CL or 3C protease, e.g., a SARS-COV2-3CL viral protease represented by SEQ ID NO: 1, wherein the cysteine at position 145 of SEQ ID NO: 1 has a non-naturally occurring covalent modification resulting from a reaction, e.g., an in vivo reaction, between an exogenous nitrile modifier having a nitrile function and the cysteine at position 145 of SEQ ID NO: 1, and wherein the sulfur atom at the cysteine residue and the nitrile of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein the engineered -3CL protease does not retain the protease activity of the unmodified -3CL or 3C protease.

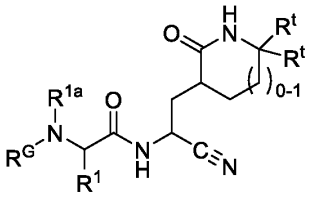
[000165] In some embodiments, the engineered SARS-COV2-3CL viral protease substantially prevents viral replication of SARS-COV2. In other embodiments, the enzymatic inhibition IC_{50} of the exogenous nitrile modifier for SEQ ID NO: 1 is less than, for example, 20 micromolar.

[000166] In further embodiments, the thioimidate adduct resulting from a reaction between the exogenous nitrile modifier and the cysteine at position 145 of SEQ ID NO: 1 may, for example, be represented by:



; wherein IR is the exogenous nitrile modifier after undergoing the reaction.

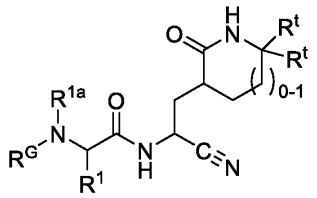
[000167] Also disclosed herein is an engineered SARS-COV2-3CL viral protease represented by SEQ ID NO: 1, wherein the cysteine at position 145 of SEQ ID NO: 1 has a non-naturally occurring covalent modification resulting from a reaction between an exogenous nitrile modifier, and the cysteine at position 145 of SEQ ID NO: 1, wherein the exogenous nitrile modifier is represented by:



wherein the sulfur atom at the cysteine residue and the -C≡N of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;
R^G is –C(O)R^B;
R^B is C_1-C_6alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m, wherein R^m is selected for each occurrence from H or C_{1-3}alkyl (optionally substituted by one, two or three halo)); or a 8-10 membered bicyclic heteroaryl (optionally substituted by one, two, or three substituents each independently selected from halo or methoxy);
R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl;
R^{1a} is H; or
R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic, bicyclic or spirocyclic heterocycle optionally substituted by one or two substituents on a free carbon each selected from methyl, halo or CF_3.

[000168] Also disclosed herein is a compound represented by



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

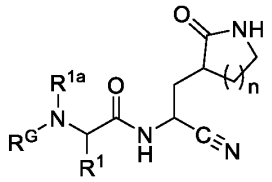
R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;
R^G is –C(O)R^B;
R^B is C_1-C_6alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m, wherein R^m is selected for each occurrence from H or C_{1-3}alkyl (optionally substituted by one, two or three halo)); or a 8-10 membered bicyclic heteroaryl (optionally substituted by one, two, or three substituents each independently selected from halo or methoxy);

R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl;

R^{1a} is H; or

R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic, bicyclic or spirocyclic heterocycle optionally substituted by one or two substituents on a free carbon each selected from methyl, halo or CF_3.

[000169] Also disclosed herein in an engineered SARS-COV2-3CL viral protease represented by SEQ ID NO: 1, wherein the cysteine at position 145 of SEQ ID NO: 1 has a non-naturally occurring covalent modification resulting from an in vivo reaction between an exogenous -C≡N modifier and the cysteine at position 145 of SEQ ID NO: 1, wherein the exogenous -C≡N modifier is represented by:



wherein the sulfur atom at the cysteine residue and the -C≡N of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;

R^G is –C(O)R^B;

R^B is C_1-C_6alkyl or 8-10 membered bicyclic heteroaryl; wherein C_1-C_6alkyl may optionally be substituted by one, two or three R^{B1}; and wherein the heteroaryl may optionally be substituted by one, two, or three halo;

R^{B1} is independently selected for each occurrence from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m;

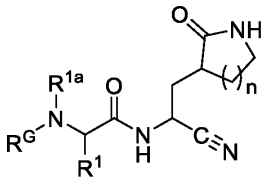
R^m is independently selected for each occurrence from hydrogen or C_{1-3}alkyl (optionally substituted by one, two or three halo);

n is 1 or 2;

R^{1a} is hydrogen; or

R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic or bicyclic heterocycle optionally substituted on a free carbon by one or two substituents each independently selected from the group consisting of CH_3, halo, and CF_3.

[000170] In another embodiment, disclosed herein is a compound represented by:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;

R^G is –C(O)R^B;

R^B is C_1-C_6alkyl or 8-10 membered bicyclic heteroaryl; wherein C_1-C_6alkyl may optionally be substituted by one, two or three R^{B1}; and wherein the heteroaryl may optionally be substituted by one, two, or three halo;

R^{B1} is independently selected for each occurrence from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m;

R^m is independently selected for each occurrence from hydrogen or C_{1-3}alkyl (optionally substituted by one, two or three halo);

n is 1 or 2;

R^{1a} is hydrogen; or

R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic or bicyclic heterocycle optionally substituted on a free carbon by one or two substituents each independently selected from the group consisting of CH_3, halo, and CF_3.

[000171] Sequence details for SEQ ID NO: 1 are indicated below.

SEQ ID NO:	Origin	Sequence
1	SARS-CoV-2 (COVID-19)	SGFRKMAFPSGKVEGCMVQVTCGTTTLNGLWLDDTVYCPRHVI CTAEDMLNPNYEDLLIRKSNHSFLVQAGNVQLRVIGHSMQNCLL RLKVDTSNPKTPKYKFVRIQPGQTFSVLACYNGSPSGVYQCAMR PNHTIKGSFLNGSCGSVGFNIDYDCVSFCYMHHMELPTGVHAGT DLEGKFYGPFVDRQTAQAAGTDTTITLNVLAWLYAAVINGDRW FLNRFTTTLNDFNLVAMKYNYEPLTQDHVDILGPLSAQTGIAVL DMCAALKELLQNGMNGRTILGSTILEDEFTPFDVVRQCSGVTFQ

IV. Pharmaceutical Compositions and Kits

[000172] Another aspect of the disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier. In particular, the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

[000173] Exemplary pharmaceutical compositions of this disclosure may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compound of the disclosure, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The

active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[000174] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, *e.g.,* conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.,* water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the disclosure, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[000175] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[000176] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative,

disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well-known in the pharmaceutical-formulating art.

[000177] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[000178] Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[000179] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[000180] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically

acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[000181] The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[000182] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[000183] Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[000184] Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain

antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[000185] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants

[000186] In another aspect, the disclosure provides enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac

and copal collophorium, and several commercially available enteric dispersion systems (e. g. , Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

[000187] Advantageously, the disclosure also provides kits for use by a e.g. a consumer in need of 3CL inhibitor. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to mediate, reduce or prevent inflammation. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well-known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[000188] It may be desirable to provide a memory aid on the kit, *e.g.,* in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.,* as follows “First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . “ etc. Other

variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

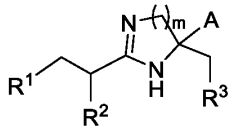
[000189] Also contemplated herein are methods and compositions that include a second active agent or administering a second active agent. For example, in addition to having a viral infection, a subject or patient can further have viral infection- or virus-related co-morbidities, i.e., diseases and other adverse health conditions associated with, exacerbated by, or precipitated by being infected by a virus. Contemplated herein are disclosed compounds in combination with at least one other agent that has previously been shown to treat these virus-related conditions.

V. Further Embodiments of the Disclosure

1. Contemplated Embodiment

[000190] In one aspect, the compositions, compounds and methods of the present disclosure may be described in one embodiment as follows:

1. A viral protease inhibitor compound represented by:



Formula I,

wherein:

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10 membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $–(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a reversible or irreversible warhead;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

m is 1 or 2; and

pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

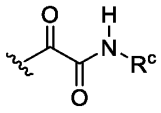
2. A is a reversible or irreversible warhead selected from the group consisting of cyano, $–C(O)R^D$, $–C(O)CH_2N(R^bR^c)$, $–C(O)CH_2OC(O)R^D$, $–C(O)C(O)R^D$, and $–(CH=CH)C(O)OR^D$, wherein

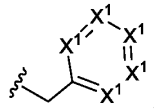
R^D is selected from the group consisting of hydrogen, $–N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl, and 5-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

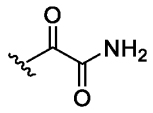
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and 5-10 membered aryl and 5-10 membered heteroaryl, wherein R^E may optionally be

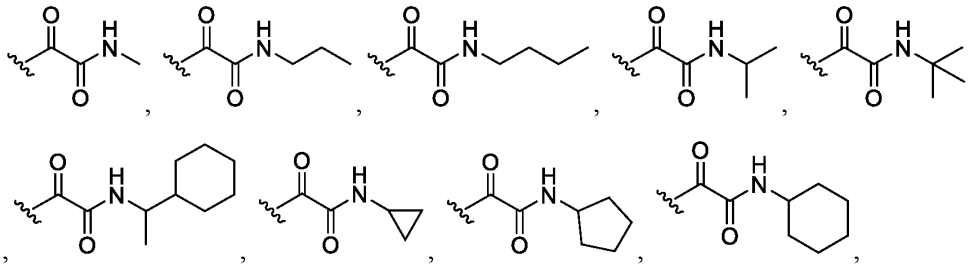
substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy; and

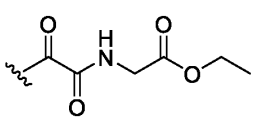
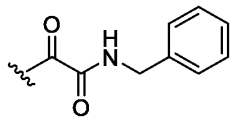
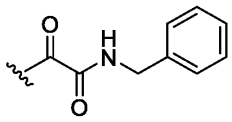
R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

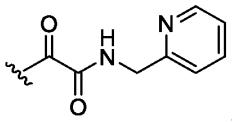
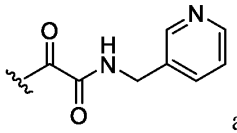
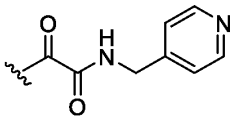
3. A is a reversible warhead  , wherein R^c is selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), C_1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

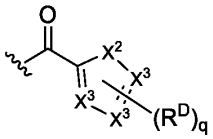
4. R^c is  , wherein X^1 is independently selected, for each occurrence, from N and CH.

5. A is a reversible warhead selected from the group consisting of  ,



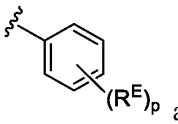
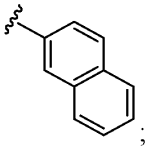
 ,  ,  ,

 ,  and  .

6. A is a reversible warhead  , wherein

X^2 is selected from the group consisting of NH, O and S;

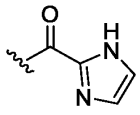
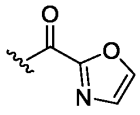
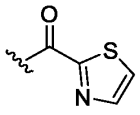
X^3 is independently selected, for each occurrence, from N and CH;

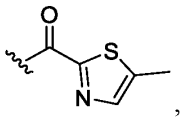
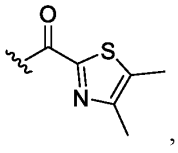
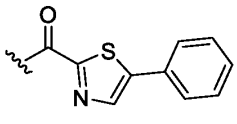
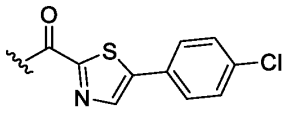
R^D is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl,  and  ;

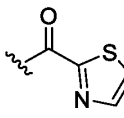
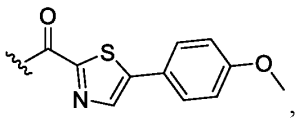
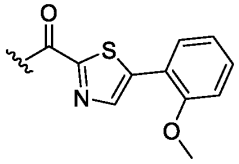
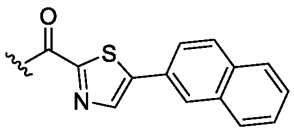
R^E is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, C_1-C_8alkyl and C_1-C_8alkoxy;

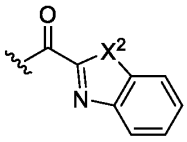
p is selected from 0, 1 and 2; and

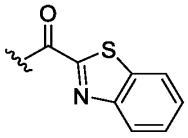
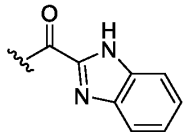
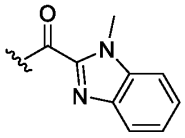
q is selected from 0, 1 and 2.

7. A is selected from the group consisting of  ,  ,  ,

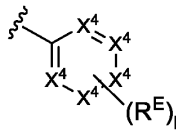
 ,  ,  ,  ,




and


8. A is a reversible warhead  , wherein X^2 is selected from the group consisting of NH, NR^P, O and S, wherein R^P is C_1-C_8alkyl.

9. A is a reversible warhead  ,  and  .

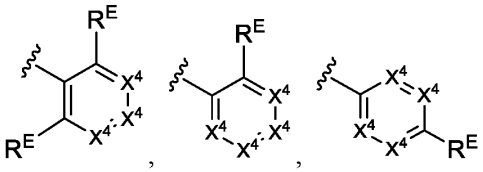
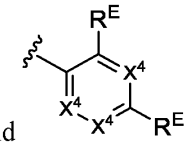
10. A is an irreversible warhead $-C(O)CH_2OC(O)R^D$, wherein

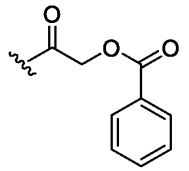
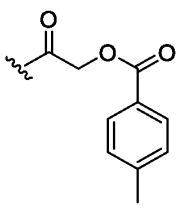
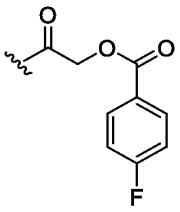
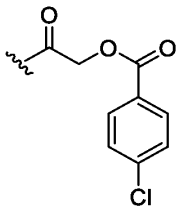
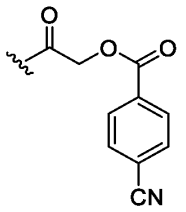
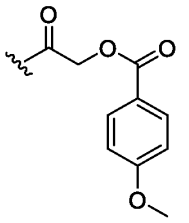
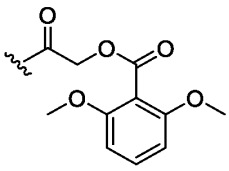
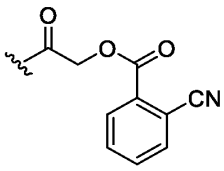
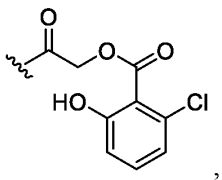
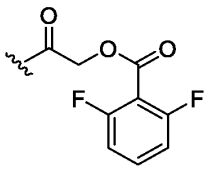
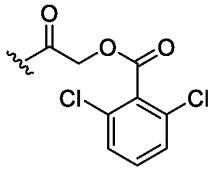
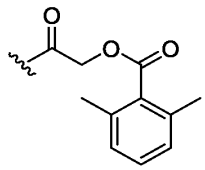
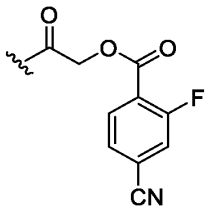
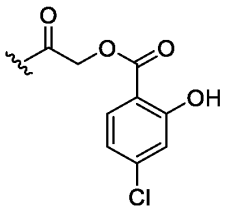
R^D is selected from the group consisting of  , C_1-C_8alkyl and C_3-C_6cycloalkyl;

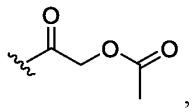
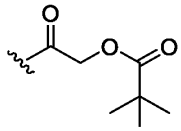
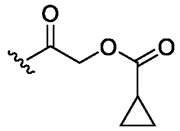
X^4 is independently selected, for each occurrence, from CH and N;

R^E is independently selected, for each occurrence, from the group consisting of halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-CF_3$, $-OCF_3$ and $-SCF_3$; and

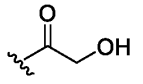
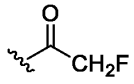
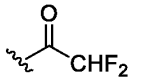
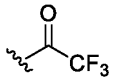
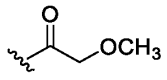
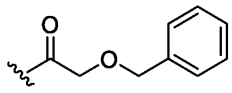
p is selected from 0, 1 and 2.

11. R^D is selected from the group consisting of  , and  .

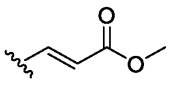
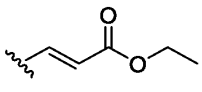
12. A is an irreversible warhead selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

13. A is an irreversible warhead selected from the group consisting of  ,  and  .

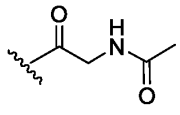
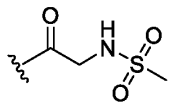
14. A is a reversible or irreversible warhead $-C(O)R^D$, wherein R^D is selected from the group consisting of hydrogen, $-CH_2OH$, $-CH_2OR'$ and $-CH_xF_y$, wherein R' is selected from the group consisting of C_1-C_8alkyl, -(C_1-C_8alkyl)-(5-10 membered aryl), C_1-C_8heteroalkyl, C_3-C_6cycloalkyl and 5-10 membered aryl, wherein x is 0, 1 or 2; y is 1, 2 or 3; and the sum of x and y is 3.

15. A is a reversible or irreversible warhead selected from the group consisting of  ,  ,  ,  ,  ,  and  .

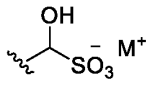
16. A is a reversible or irreversible warhead $-(CH=CH)C(O)OR^D$, wherein R^D is C_1-C_8alkyl.

17. A is an irreversible warhead selected from  and  .

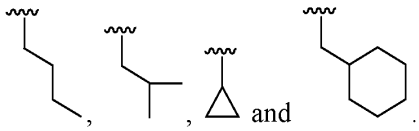
18. A is a reversible or irreversible warhead $-C(O)CH_2N(R^bR^c)$.

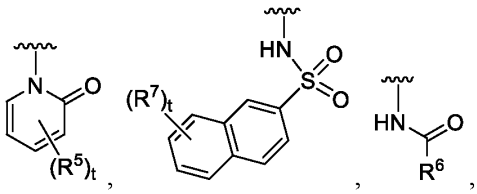
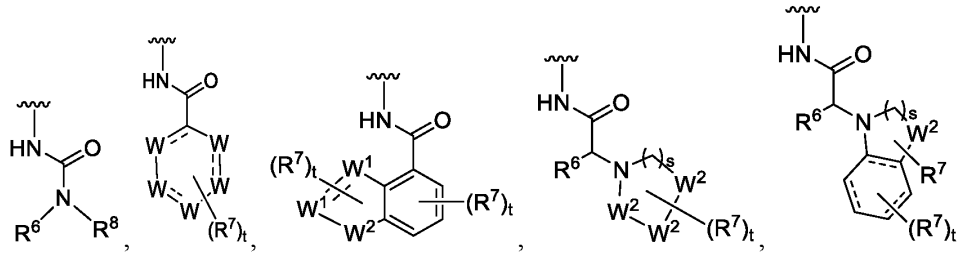
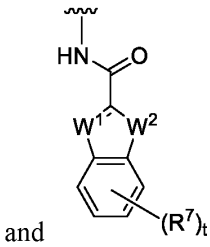
19. A is a reversible or irreversible warhead selected from  and  .

20. A is a reversible or irreversible warhead


, wherein M is selected from Na and K.

21. A is cyano.

22. R^1 is selected from the group consisting of  .

23. R^2 is selected from the group consisting of  ,  , 
and , wherein

denotes a bond that may be a single or double bond;

R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^6 is C_1-C_8alkyl;

R^7 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

R^8 is selected from the group consisting of 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

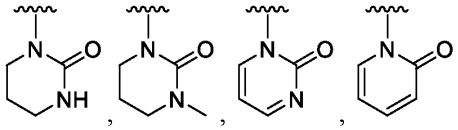
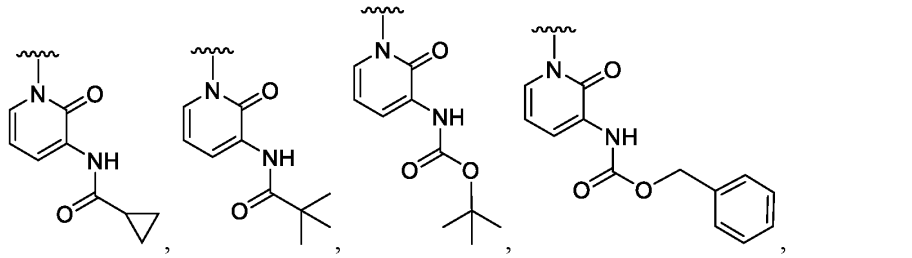
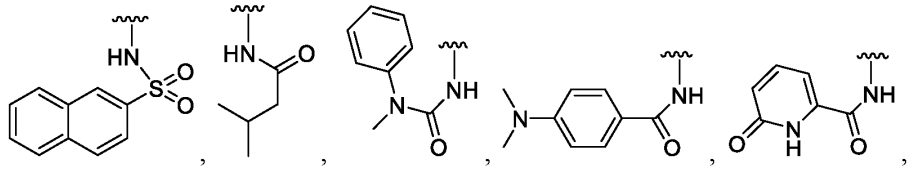
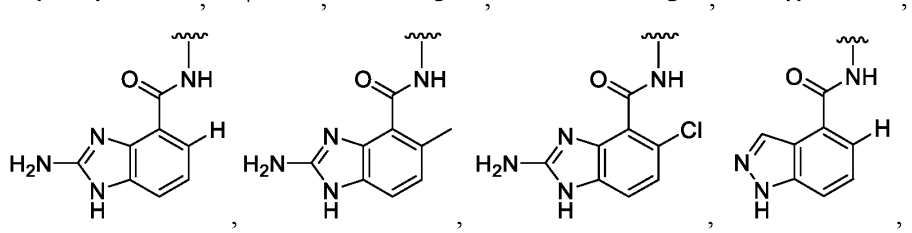
W^1 is selected from CH and N;

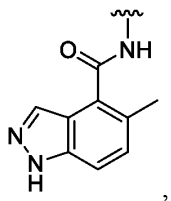
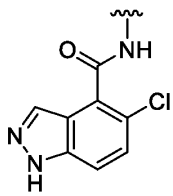
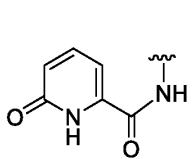
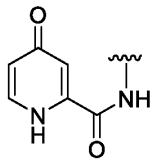
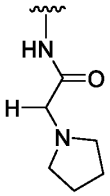
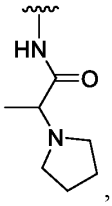
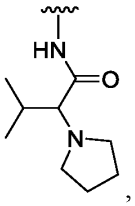
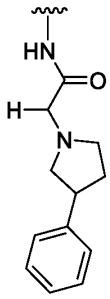
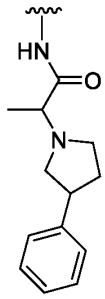
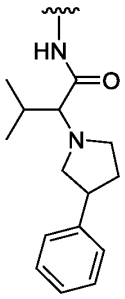
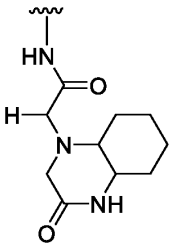
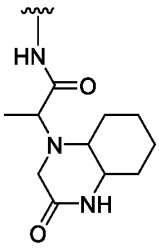
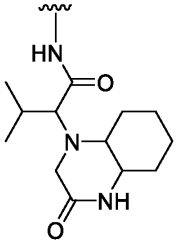
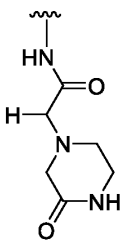
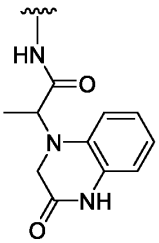
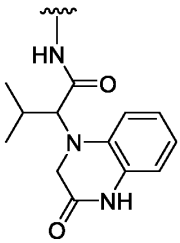
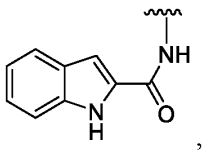
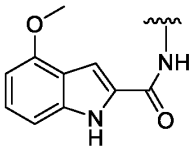
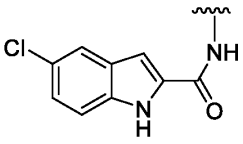
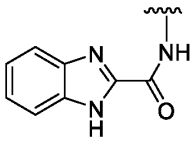
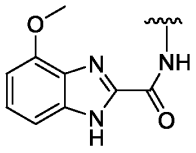
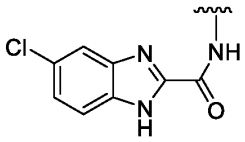
W^2 is selected from the group consisting of CH_2, O, NH and S;

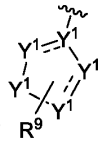
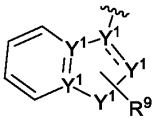
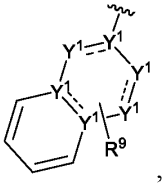
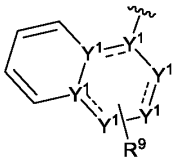
W is selected from W^1 and W^2;

s is selected from 1 and 2; and

t is selected from 0, 1, 2 and 3.

24. R^2 is selected from the group consisting of  ,  ,  , 






















and


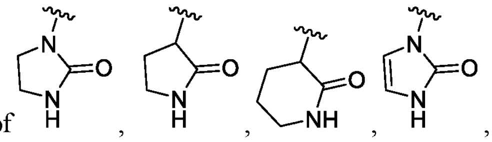
25. R^3 is selected from the group consisting of  ,  ,  ,  ,  , and .

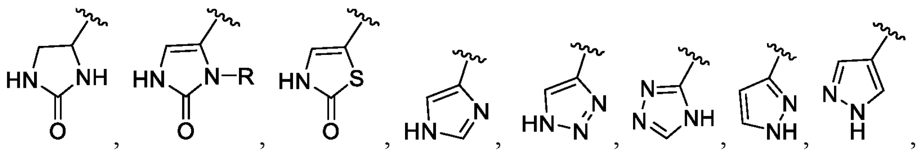
wherein

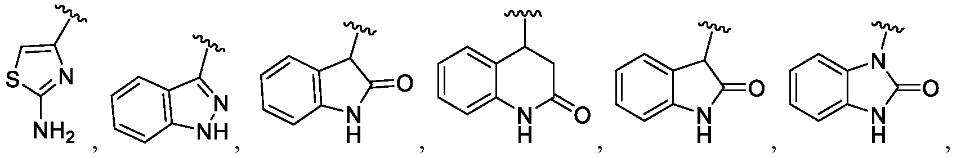
------- denotes a bond that may be a single or double bond;

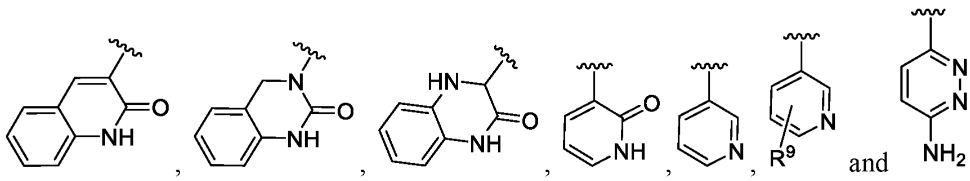
Y^1 is selected from the group consisting of CH, CH_2, N, NH, O and S;

R^9 is selected from the group consisting of halogen, hydroxyl, oxo, $-NH_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$ and $-OCH_2CH_3$.

26. R^3 is selected from the group consisting of 

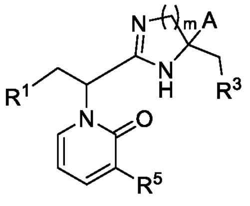






.

27. The viral protease inhibitor compound is represented by



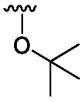
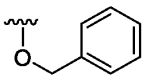
Formula I-A,

wherein:

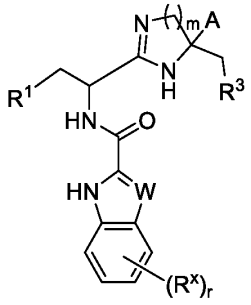
R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl; and

m is selected from 1 and 2.

28. R^y is selected from the group consisting of hydrogen,  ,  ,  and  .

29. The viral protease inhibitor compound is represented by



Formula I-B,

wherein

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

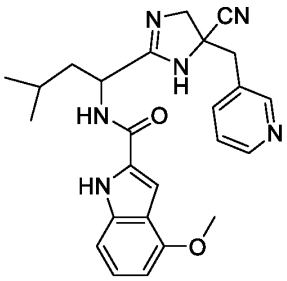
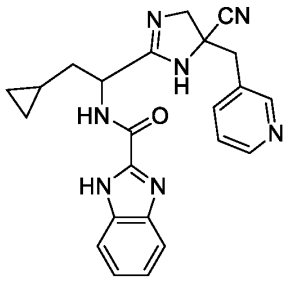
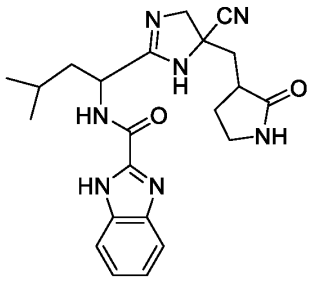
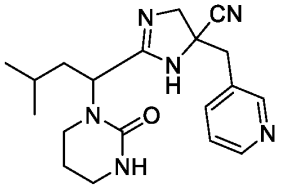
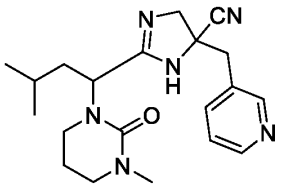
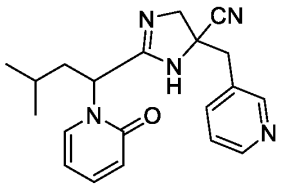
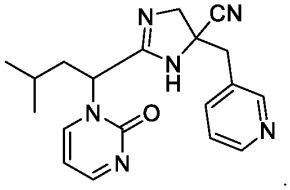
W is CH or N;

m is selected from 1 and 2; and

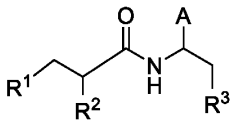
r is selected from 0, 1, 2 and 3.

30. R^x is $-OCH_3$.

31. A viral protease inhibitor compound selected from the group consisting of


,

,

,

,

,

and

.

32. A viral protease inhibitor compound represented by:



Formula II,

wherein

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10 membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $–(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a reversible or irreversible warhead;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A; and

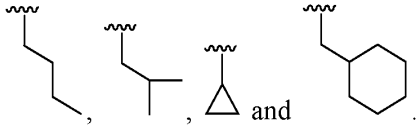
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

33. A is a reversible or irreversible warhead selected from the group consisting of cyano, $–C(O)R^D$, $–C(O)CH_2N(R^bR^c)$, $–C(O)CH_2OC(O)R^D$, $–C(O)C(O)R^D$, and $–(CH=CH)C(O)OR^D$, wherein

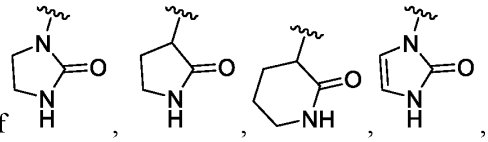
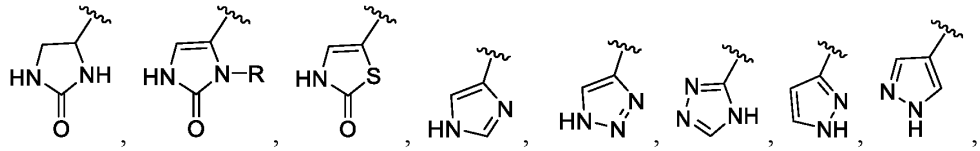
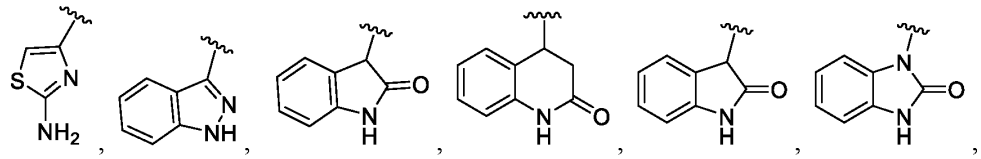
R^D is selected from the group consisting of hydrogen, –N(R^bR^c), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl, and 5-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

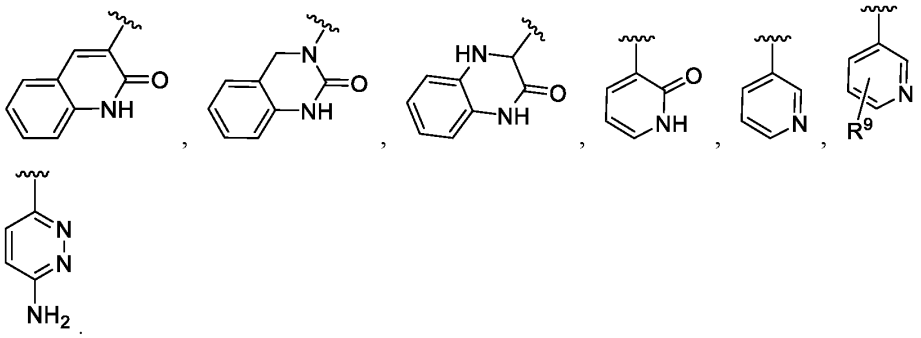
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and 5-10 membered aryl and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy; and

R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

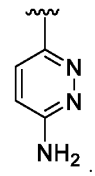
34. R^1 is selected from the group consisting of  .

35. R^3 is a 5-10 membered heterocycle.

36. R^3 is selected from the group consisting of  ,  ,  .

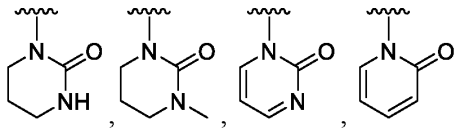


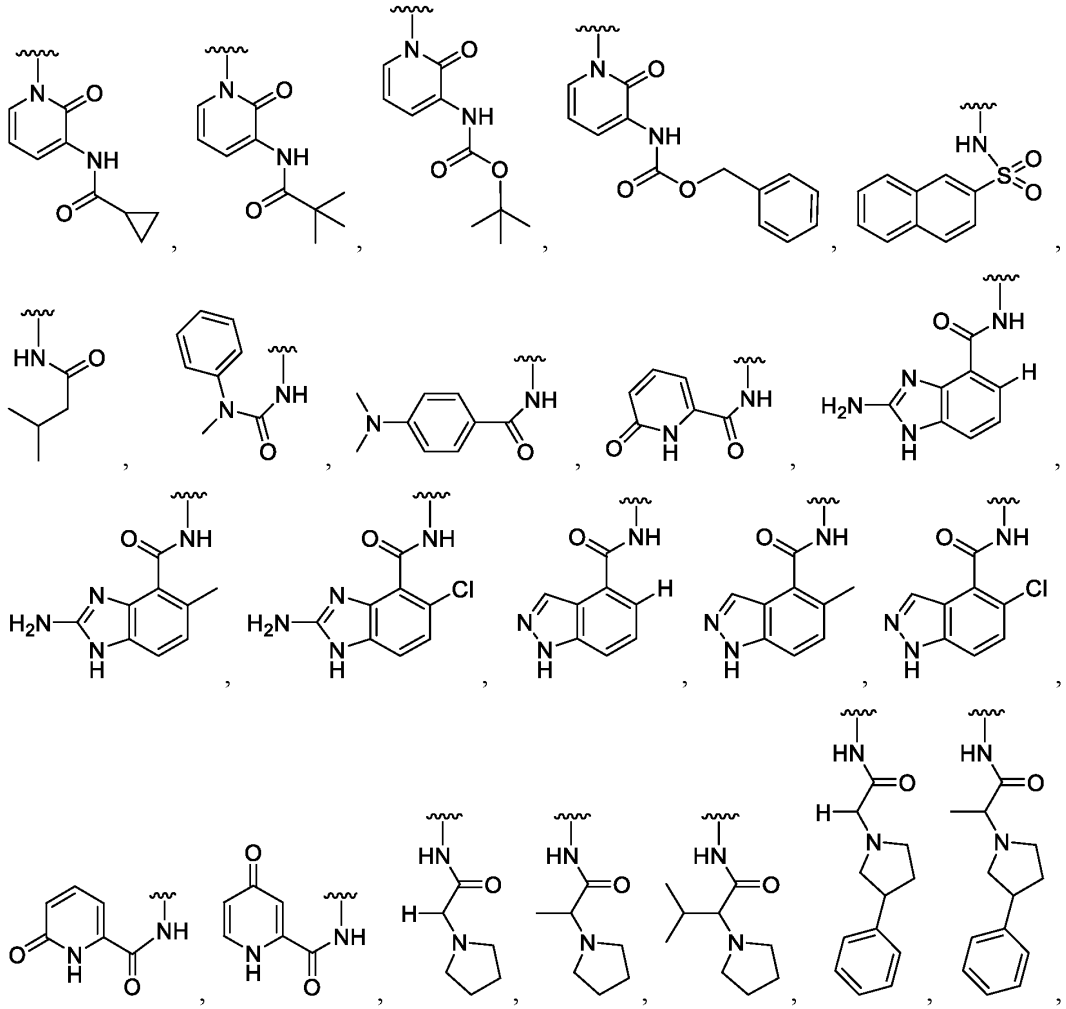
and

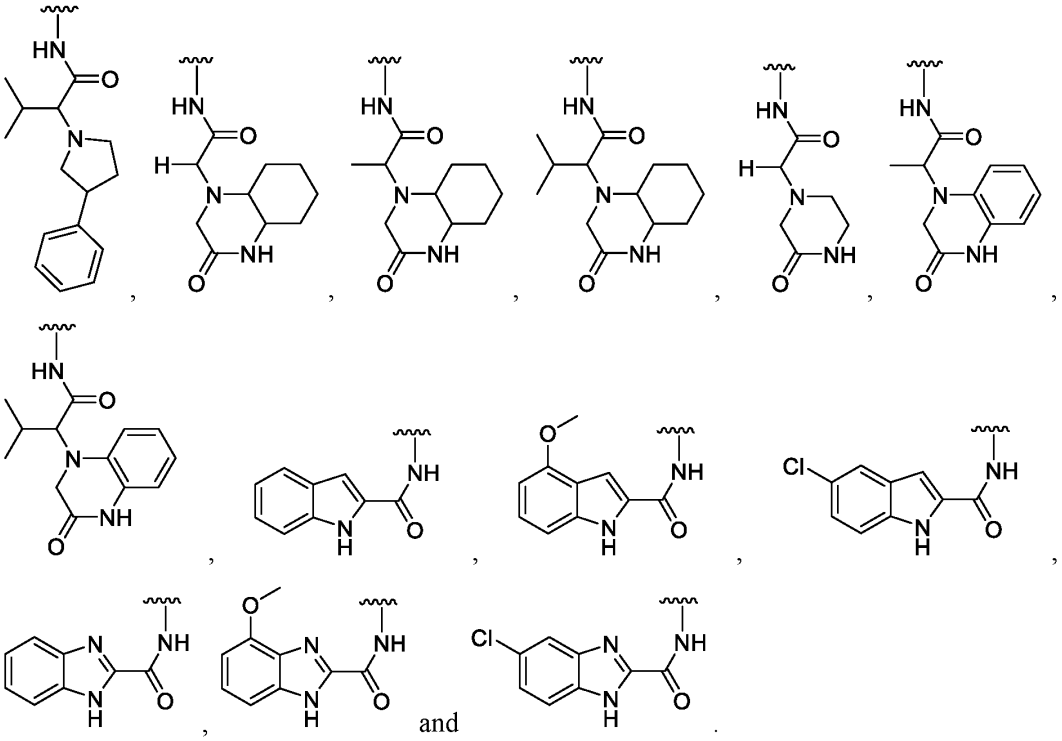


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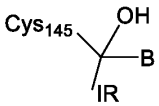
37. R^2 is selected from the group consisting of







38. A reversible conjugate represented by:



Formula IV,

wherein

Cys_{145} is cysteine at position 145 or equivalent active site cysteine on a CL or 3CL protease;

IR is a viral protease inhibitor;

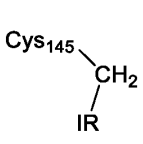
B is selected from the group consisting of $–R^D$, $–C(O)R^D$, and $–CH_2OR^D$, wherein

R^D is selected from the group consisting of hydrogen, $–N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl, and 5-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl and R^E;

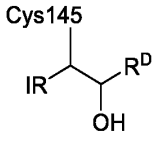
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and 5-10 membered aryl and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, C_1-C_8alkyl and C_1-C_8alkoxy; and

R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

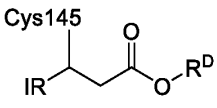
39. An irreversible conjugate represented by:



(Formula V-A),



(Formula V-B) or



(Formula V-C),

wherein

Cys_{145} is cysteine at position 145 or equivalent active site cysteine on a CL or 3CL protease;

IR is a viral protease inhibitor;

R^D is selected from the group consisting of hydrogen, –$N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl, and 5-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl and R^E;

R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and 5-10 membered aryl and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, C_1-C_8alkyl and C_1-C_8alkoxy; and

R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

40. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any compound of the embodiment.

41. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.

42. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.

43. The viral infection is a coronavirus infection.

44. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).

45. The viral infection is SARS-CoV-2.

46. The viral infection is an arenavirus infection.

48. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.

48. The viral infection is an influenza infection.

49. The influenza is influenza H1N1, H3N2 or H5N1.

50. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of a compound of the embodiment to a patient suffering from the virus, and/or contacting an effective amount of a compound of the embodiment with a virally infected cell.

51. A method of the embodiment further comprises administering another therapeutic.

52. A method of the embodiment further comprises administering an additional anti-viral therapeutic.

53. The anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, and remdesivir.

54. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

55. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, and remdesivir.

56. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of any compound of the embodiment.

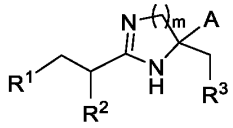
57. The compound is administered before viral exposure.

58. The compound is administered after viral exposure.

2. Contemplated Embodiment

[000191] In another aspect, the compositions, compounds and methods of the present disclosure may be described in another embodiment as follows:

1. A viral protease inhibitor compound represented by:



Formula I,

wherein:

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NH_2$, $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10 membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a reversible or irreversible warhead;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

m is 1 or 2; and

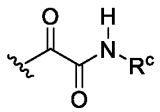
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

2. A is a reversible or irreversible warhead selected from the group consisting of cyano, –$C(O)R^D$, –$C(O)CH_2N(R^bR^c)$, –$C(O)CH_2OC(O)R^D$, –$C(O)C(O)R^D$, and –$(CH=CH)C(O)OR^D$, wherein

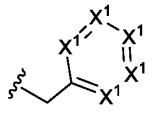
R^D is selected from the group consisting of hydrogen, –$N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl, and 5-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

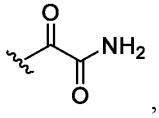
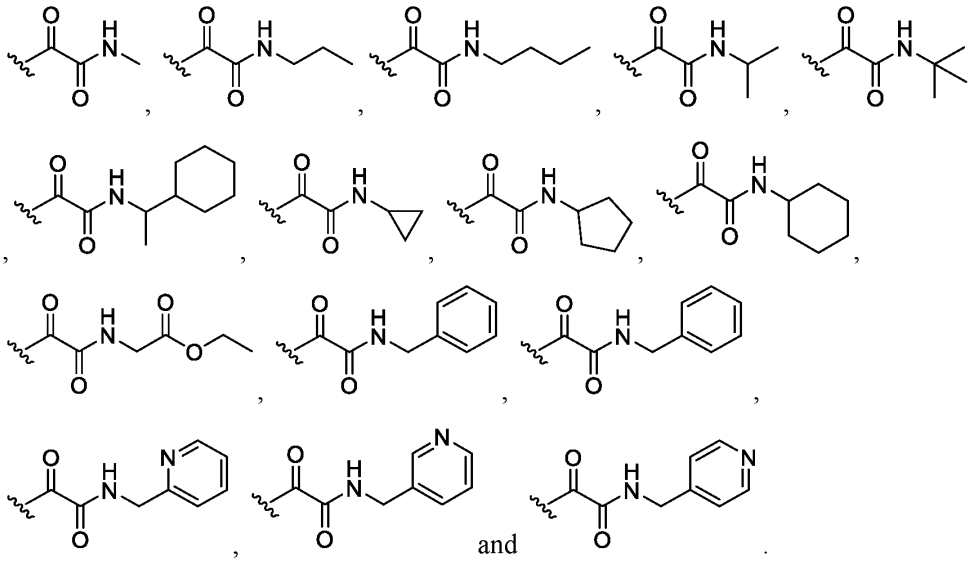
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and 5-10 membered aryl and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy; and

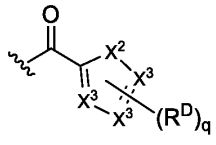
R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

3. A is a reversible warhead  , wherein R^c is selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), C_1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each

selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

4. R^c is  , wherein X^1 is independently selected, for each occurrence, from N and CH.

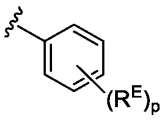
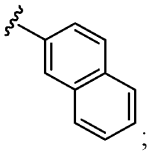
5. A is a reversible warhead selected from the group consisting of  ,

and
.

6. A is a reversible warhead  , wherein

X^2 is selected from the group consisting of NH, O and S;

X^3 is independently selected, for each occurrence, from N and CH;

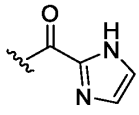
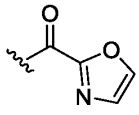
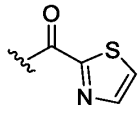
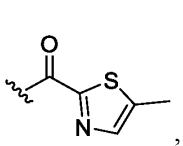
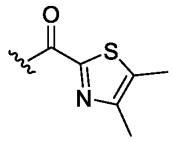
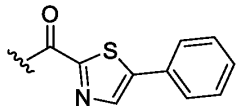
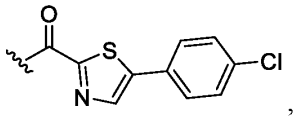
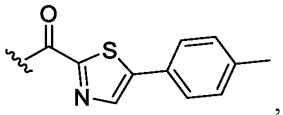
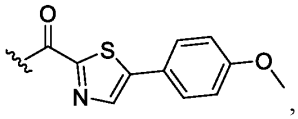
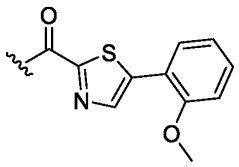
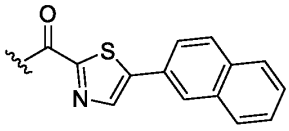
R^D is independently selected, for each occurrence, from the group consisting of

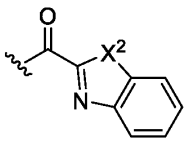
C_1-C_8alkyl,  and  ;

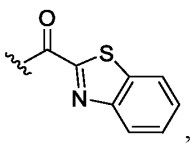
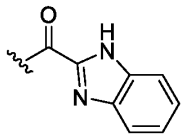
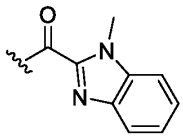
R^E is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, C_1-C_8alkyl and C_1-C_8alkoxy;

p is selected from 0, 1 and 2; and

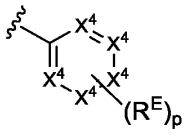
q is selected from 0, 1 and 2.

7. A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

8. A is a reversible warhead  , wherein X^2 is selected from the group consisting of NH, NR^P, O and S, wherein R^P is C_1-C_8alkyl.

9. A is a reversible warhead  ,  , and  .

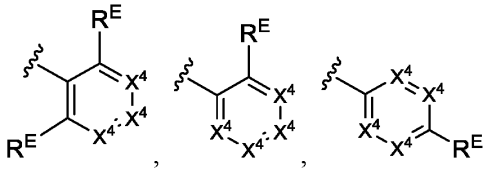
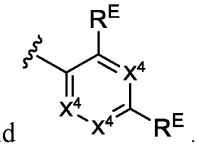
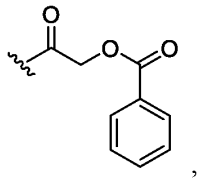
10. A is an irreversible warhead $-C(O)CH_2OC(O)R^D$, wherein

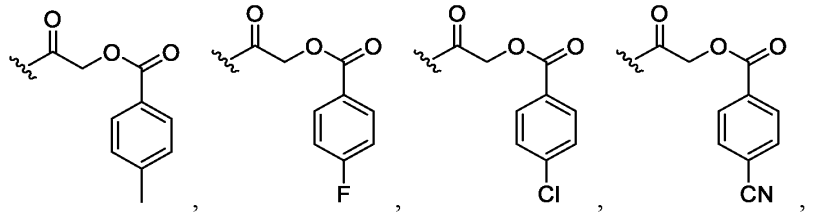
R^D is selected from the group consisting of  , C_1-C_8alkyl and C_3-C_6cycloalkyl;

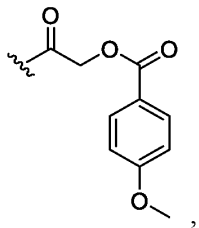
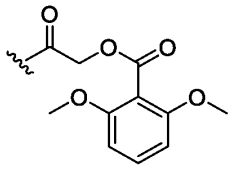
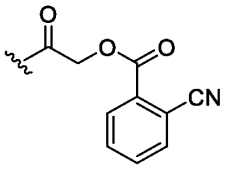
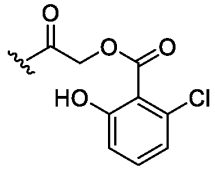
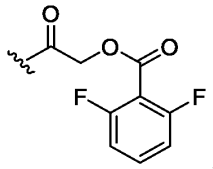
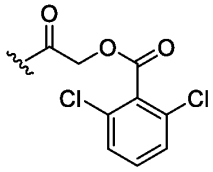
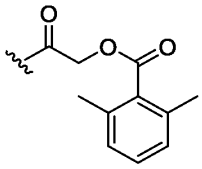
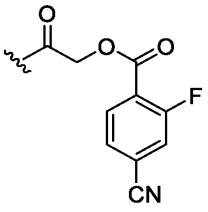
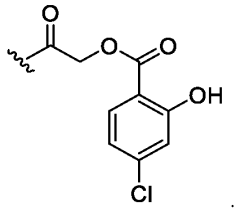
X^4 is independently selected, for each occurrence, from CH and N;

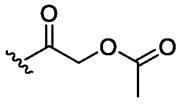
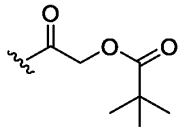
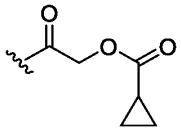
R^E is independently selected, for each occurrence, from the group consisting of halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-CF_3$, $-OCF_3$ and $-SCF_3$; and

p is selected from 0, 1 and 2.

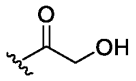
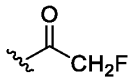
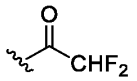
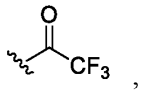
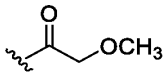
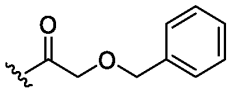
11. R^D is selected from the group consisting of  ,  and  .

12. A is an irreversible warhead selected from the group consisting of  .

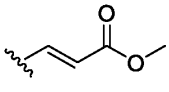
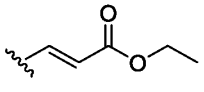

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and

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13. A is an irreversible warhead selected from the group consisting of  ,

and

.

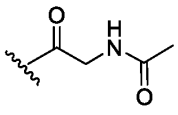
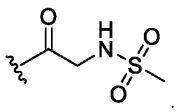
14. A is a reversible or irreversible warhead $-C(O)R^D$, wherein R^D is selected from the group consisting of hydrogen, $-CH_2OH$, $-CH_2OR'$ and $-CH_xF_y$, wherein R' is selected from the group consisting of C_1-C_8alkyl, -(C_1-C_8alkyl)-(5-10 membered aryl), C_1-C_8heteroalkyl, C_3-C_6cycloalkyl and 5-10 membered aryl, wherein x is 0, 1 or 2; y is 1, 2 or 3; and the sum of x and y is 3.

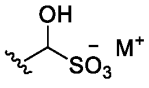
15. A is a reversible or irreversible warhead selected from the group consisting of  ,  ,  ,  ,  ,  and  .

16. A is a reversible or irreversible warhead –(CH=CH)C(O)OR^D, wherein R^D is C$_1$-C$_8$alkyl.

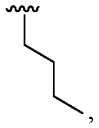
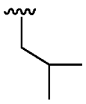
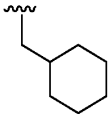
17. A is an irreversible warhead selected from  and  .

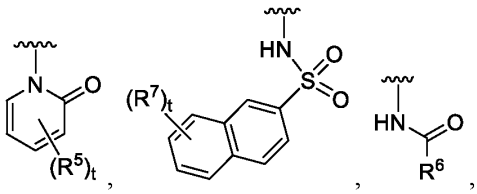
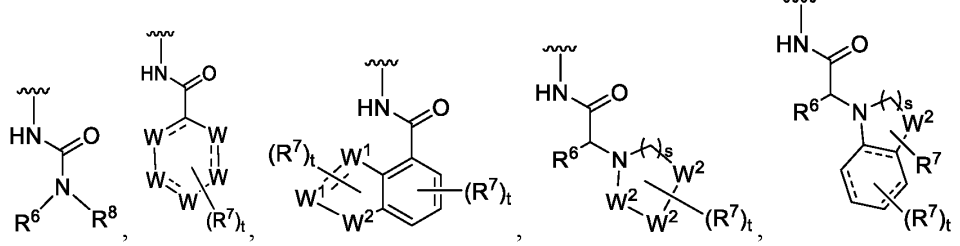
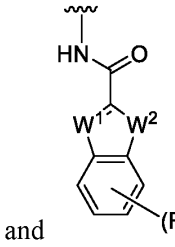
18. A is a reversible or irreversible warhead –C(O)CH$_2$N(R^{b}R^c).

19. A is a reversible or irreversible warhead selected from  and  .

20. A is a reversible or irreversible warhead  , wherein M is selected from Na and K.

21. A is cyano.

22. R^1 is selected from the group consisting of  ,  ,  and  .

23. R^2 is selected from the group consisting of  ,  ,  , and , wherein

denotes a bond that may be a single or double bond;

R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^6 is C_1-C_8alkyl;

R^7 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

R^8 is selected from the group consisting of 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

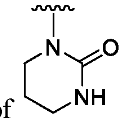
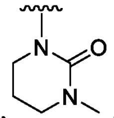
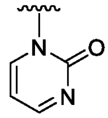
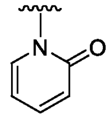
W^1 is selected from CH and N;

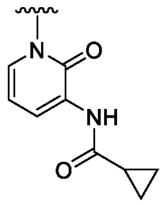
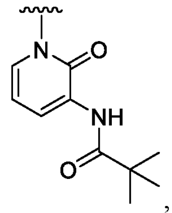
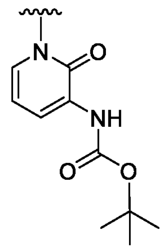
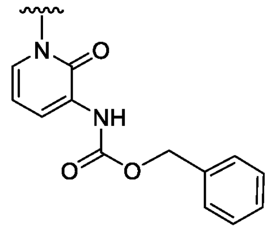
W^2 is selected from the group consisting of CH_2, O, NH and S;

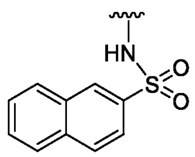
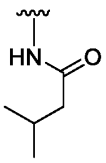
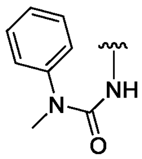
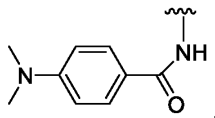
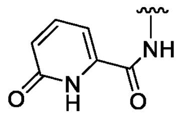
W is selected from W^1 and W^2;

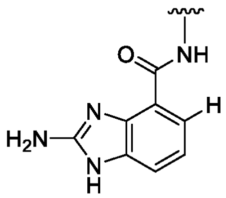
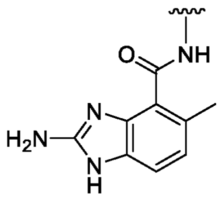
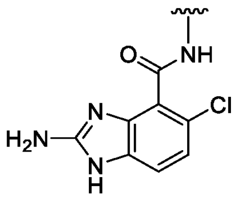
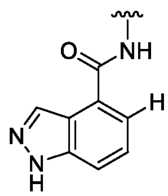
s is selected from 1 and 2; and

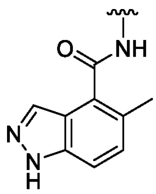
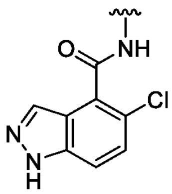
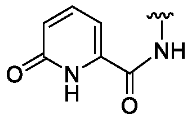
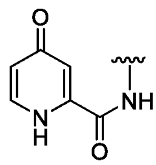
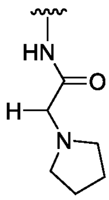
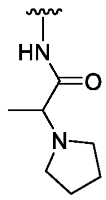
t is selected from 0, 1, 2 and 3.

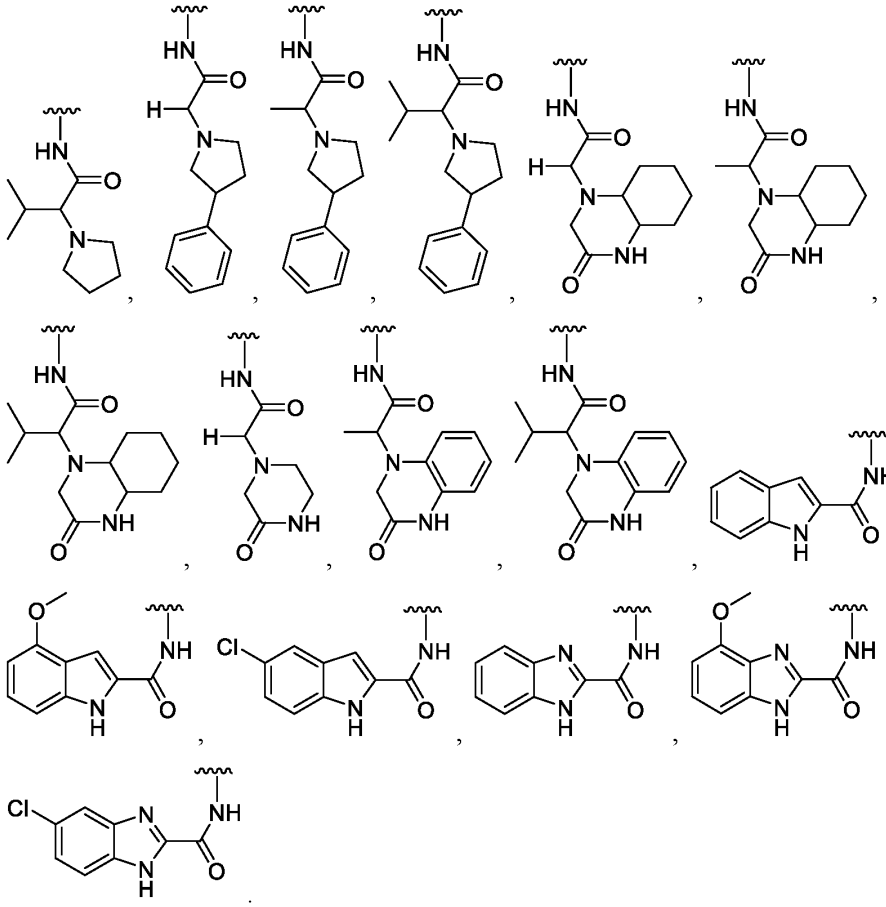
24. R^2 is selected from the group consisting of  ,  ,  ,  ,

 ,  ,  ,  ,

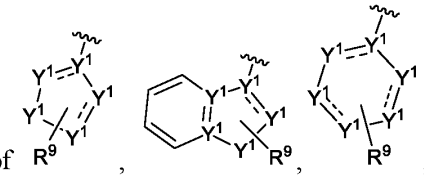
 ,  ,  ,  ,  ,

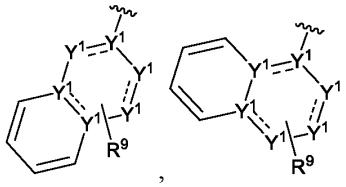
 ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,



and

25. R^3 is selected from the group consisting of 

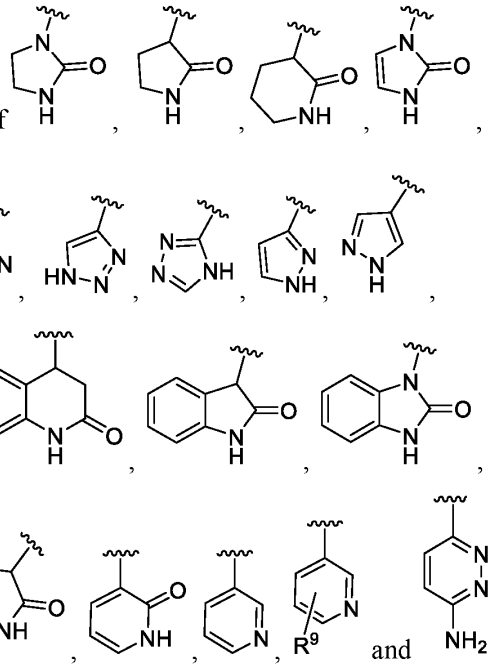


wherein

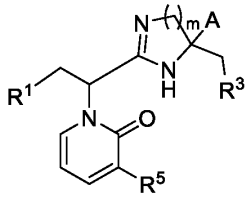
$\overline{\text{=======}}$ denotes a bond that may be a single or double bond;

Y^1 is selected from the group consisting of CH, CH_2, N, NH, O and S;

R^9 is selected from the group consisting of halogen, hydroxyl, oxo, $–NH_2$, $–N(CH_3)_2$, $–N(CH_2CH_3)_2$, $–CH_3$, $–CH_2CH_3$, $–OCH_3$ and $–OCH_2CH_3$.

26. R^3 is selected from the group consisting of 

27. The compound is represented by



Formula I-A,

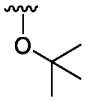
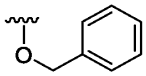
wherein:

R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered

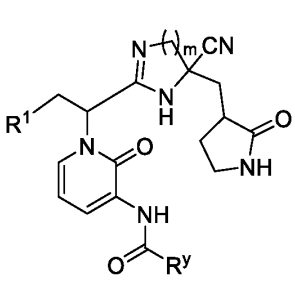
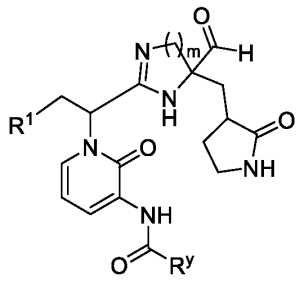
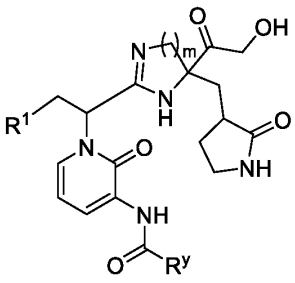
heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

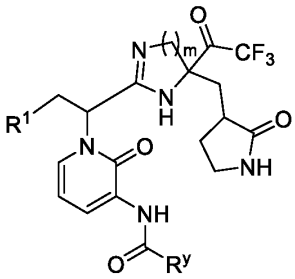
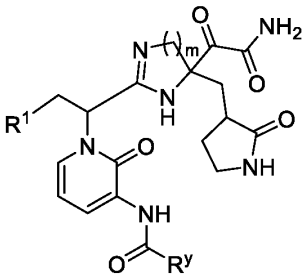
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl; and

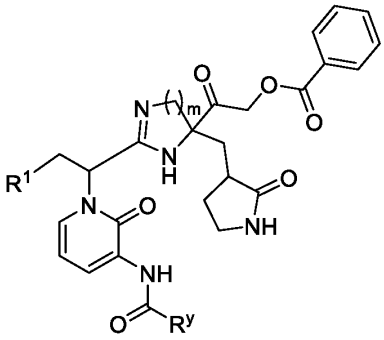
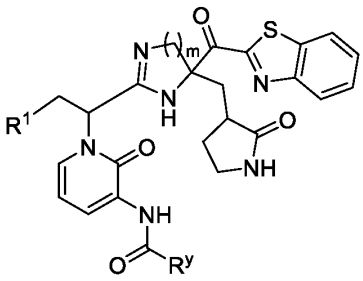
m is selected from 1 and 2.

28. R^y is selected from the group consisting of hydrogen,  ,  ,  and  .

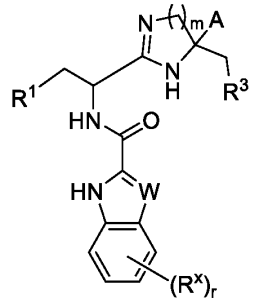
29. The compound is selected from the group consisting of:

 ,  ,  ,

 ,  ,

 , and  .

30. The compound is represented by



Formula I-B,

wherein

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

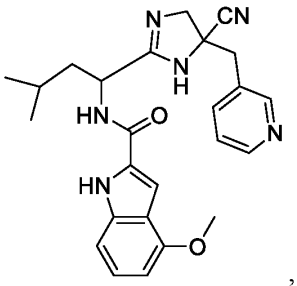
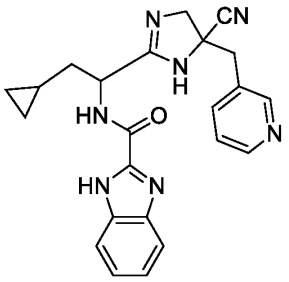
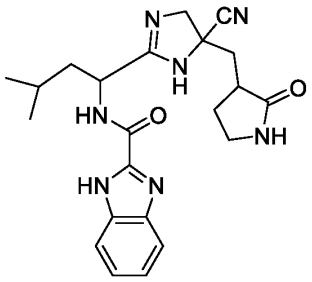
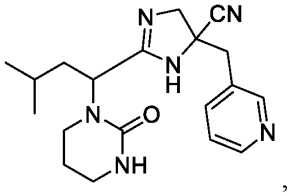
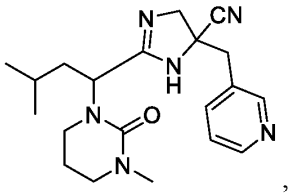
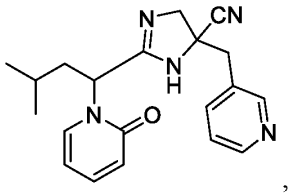
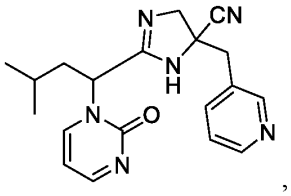
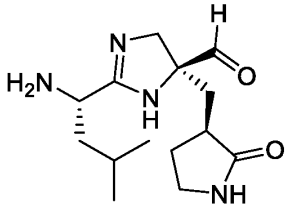
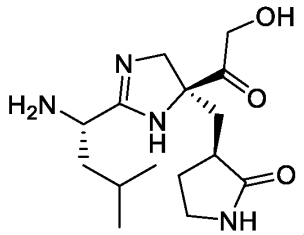
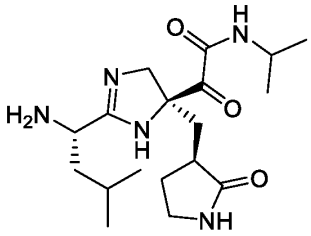
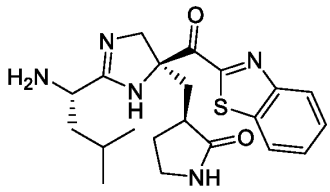
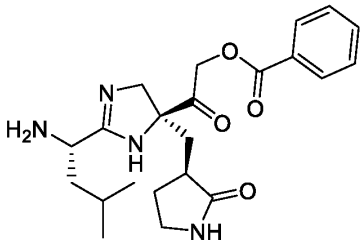
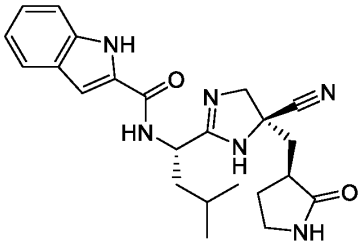
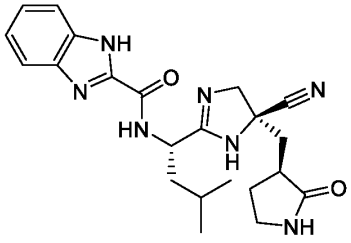
W is CH or N;

m is selected from 1 and 2; and

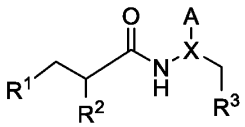
r is selected from 0, 1, 2 and 3.

31. R^x is $-OCH_3$.

32. A viral protease inhibitor compound selected from the group consisting of


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33. A viral protease inhibitor compound represented by:



Formula II,

wherein

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10 membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $–(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

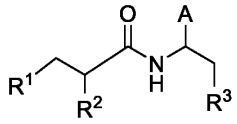
A is a reversible or irreversible warhead;

X is selected from CH and N;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A; and

pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

33. The compound is represented by:



Formula II-A,

wherein

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10 membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a reversible or irreversible warhead;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A; and

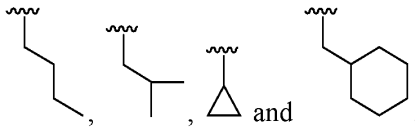
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

34. A is a reversible or irreversible warhead selected from the group consisting of cyano, –$C(O)R^D$, –$C(O)CH_2N(R^bR^c)$, –$C(O)CH_2OC(O)R^D$, –$C(O)C(O)R^D$, and –$(CH=CH)C(O)OR^D$, wherein

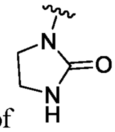
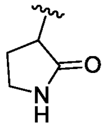
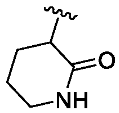
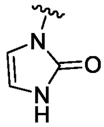
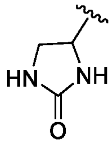
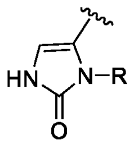
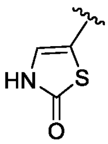
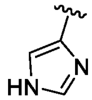
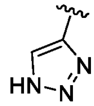
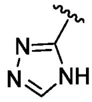
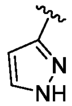
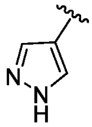
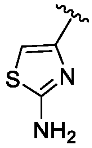
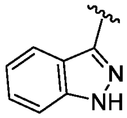
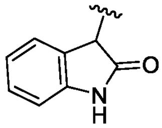
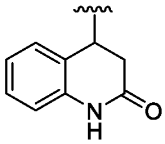
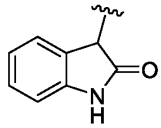
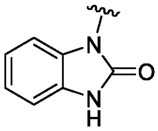
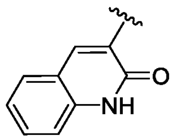
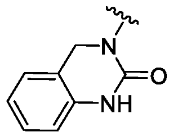
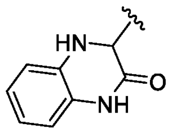
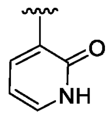
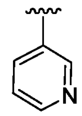
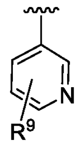
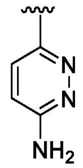
R^D is selected from the group consisting of hydrogen, –$N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl, and 5-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

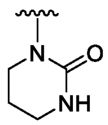
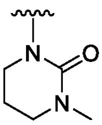
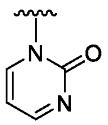
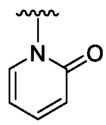
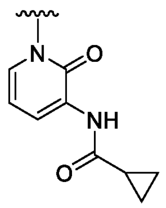
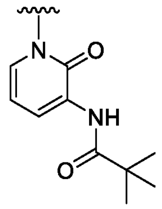
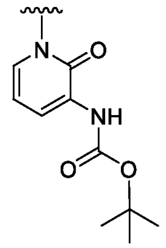
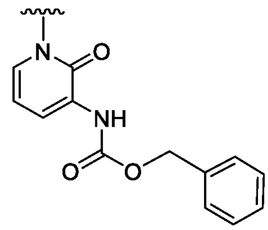
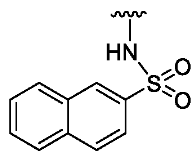
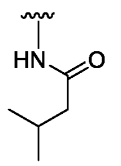
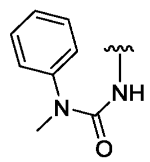
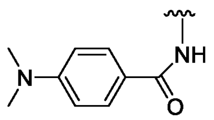
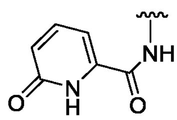
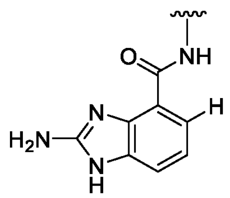
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and 5-10 membered aryl and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy; and

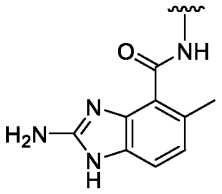
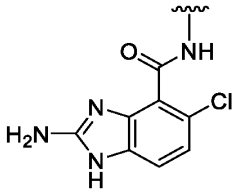
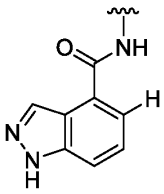
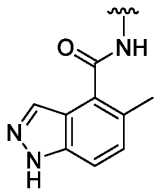
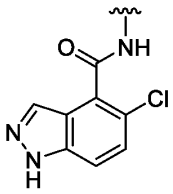
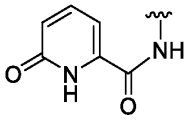
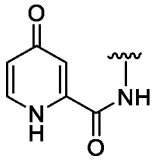
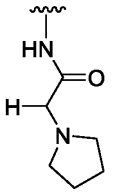
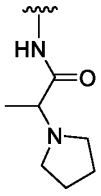
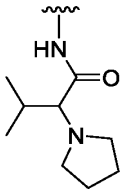
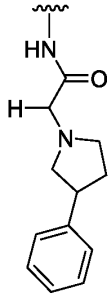
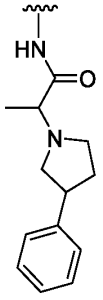
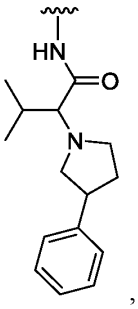
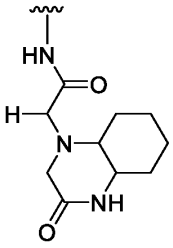
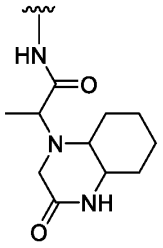
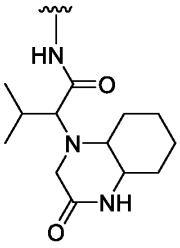
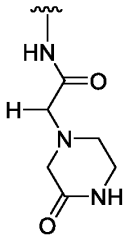
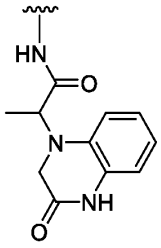
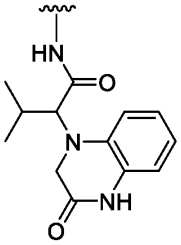
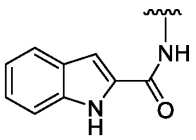
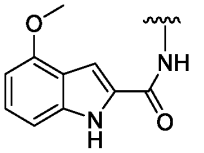
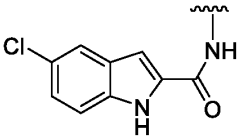
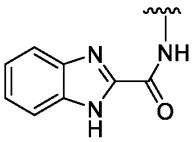
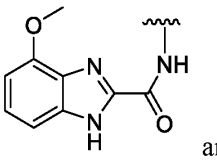
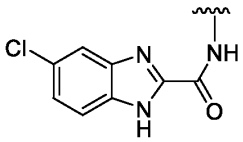
R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –$C(O)$-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

35. R^1 is selected from the group consisting of  .

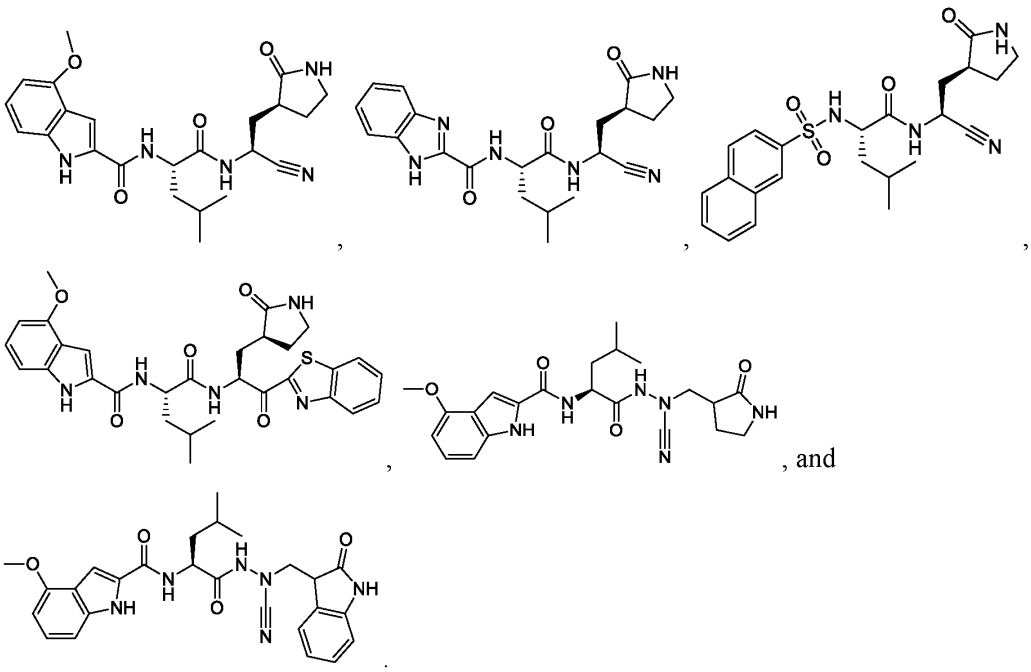
36. R^3 is a 5-10 membered heterocycle.

37. R^3 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

38. R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,


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and

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39. The compound is selected from the group consisting of:



, and

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40. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds of the embodiment.

41. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.

42. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.

43. The viral infection is a coronavirus infection.

44. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).

45. The viral infection is SARS-CoV-2.

46. The viral infection is an arenavirus infection.

47. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.

48. The viral infection is an influenza infection.

49. The influenza is influenza H1N1, H3N2 or H5N1.

50. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of any compound of the embodiment to a patient suffering from the virus, and/or contacting an effective amount of any compound of the embodiment with a virally infected cell.

51. The method further comprises administering another therapeutic.

52. The method further comprises administering an additional anti-viral therapeutic.

53. The the anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, and remdesivir.

54. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin,

ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

55. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, and remdesivir.

56. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of any compound of the embodiment.

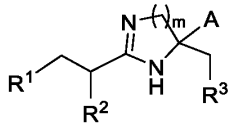
57. The compound is administered before viral exposure.

58. The compound is administered after viral exposure.

3. Contemplated Embodiment

[000192] In another aspect, the compositions, compounds and methods of the present disclosure may be described in another embodiment as follows:

1. A protease inhibitor compound represented by:



Formula I,

wherein:

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NH_2$, $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10

membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

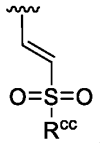
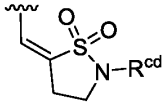
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a warhead;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

m is 1 or 2; and

pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

2. A is selected from the group consisting of cyano, $-C(O)R^D$, $-C(O)CH_2N(R^bR^c)$, $-C(O)CH_2OC(O)R^D$, $-C(O)C(O)R^D$, $-(CH=CH)C(O)OR^D$, $-(CH=CCN)C(O)OR^D$, $-(CH=CCN)C(O)(NH)R^D$, $-CH(CN)(OH)$, $-CH(CN)(NR^bR^c)$,  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, $-OR^{bb}$, $-N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered

heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

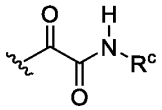
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

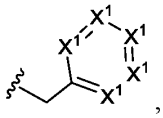
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

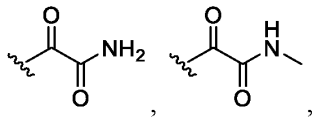
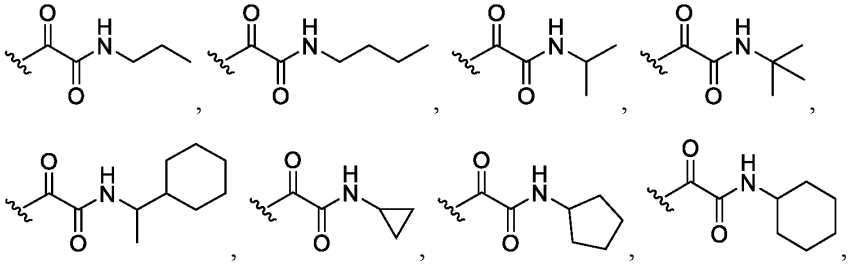
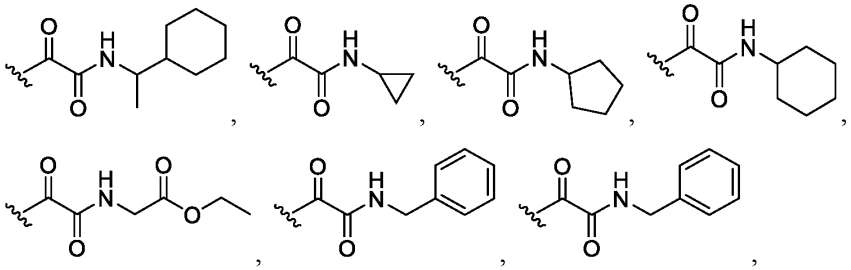
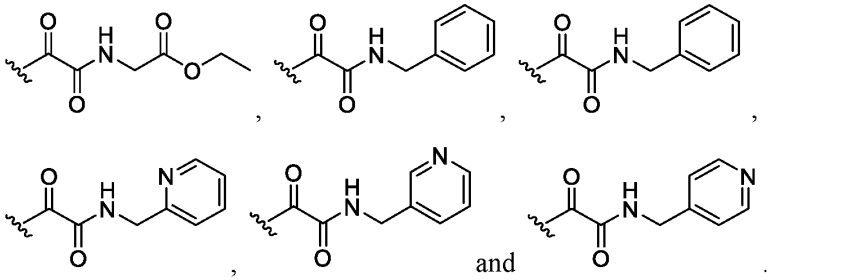
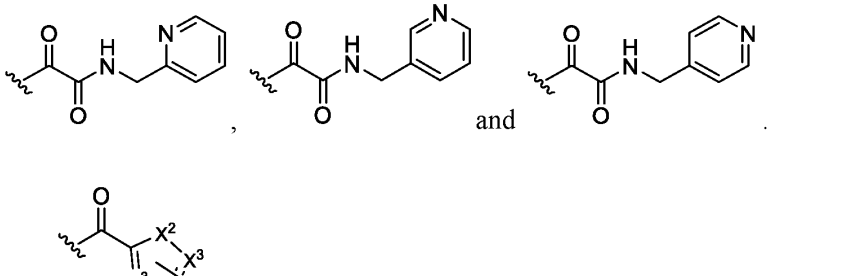
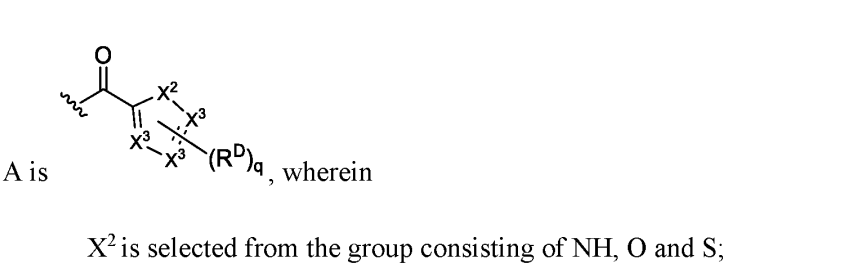
R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

3. A is a warhead represented by:  , wherein R^c is selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), C_1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

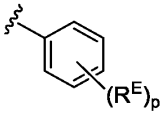
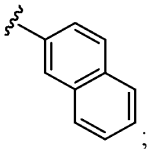
4. R^C is  , wherein X^1 is independently selected, for each occurrence, from N and CH.

5. A is selected from the group consisting of  ,  ,  ,  ,  ,  , and .

6. A is , wherein

X^2 is selected from the group consisting of NH, O and S;

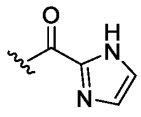
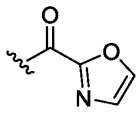
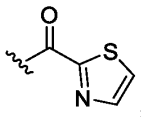
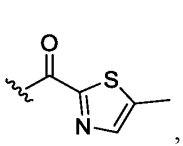
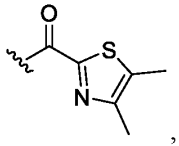
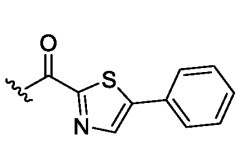
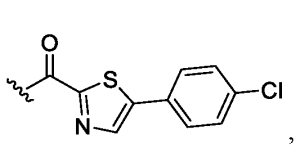
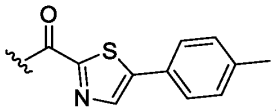
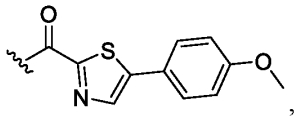
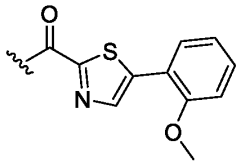
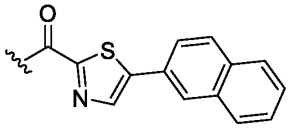
X^3 is independently selected, for each occurrence, from N and CH;

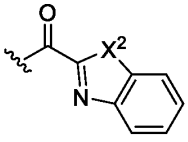
R^D is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl,  and  ;

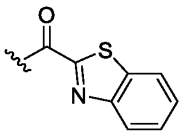
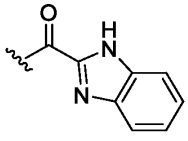
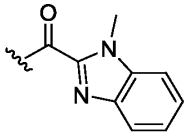
R^E is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, C_1-C_8alkyl and C_1-C_8alkoxy;

p is selected from 0, 1 and 2; and

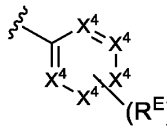
q is selected from 0, 1 and 2.

7. A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

8. A is  , wherein X^2 is selected from the group consisting of NH, NR^P, O and S, wherein R^P is C_1-C_8alkyl.

9. A is selected from the group consisting of  ,  and  .

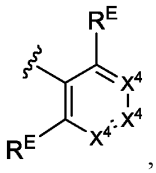
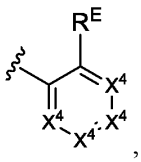
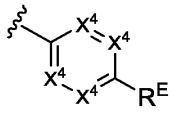
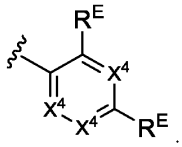
10. A is–$C(O)CH_2OC(O)R^D$, wherein

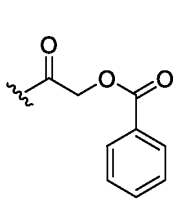
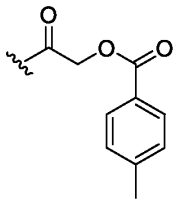
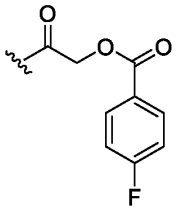
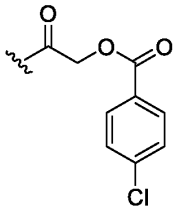
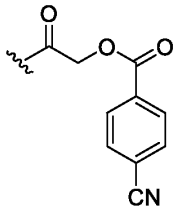
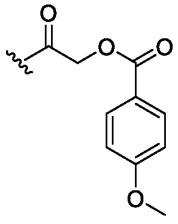
R^D is selected from the group consisting of  , C_1-C_8alkyl and C_3-C_6cycloalkyl;

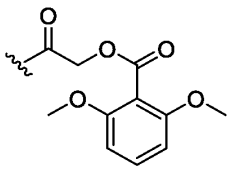
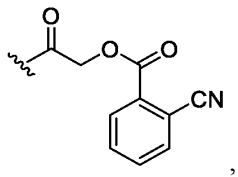
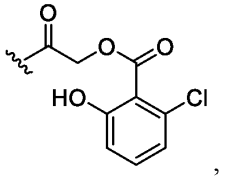
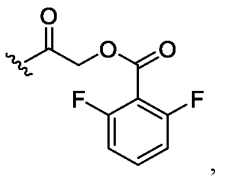
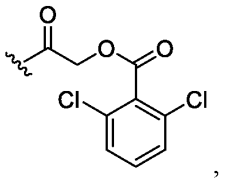
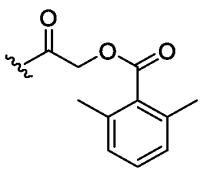
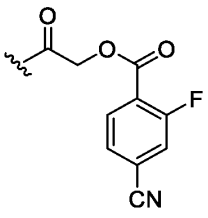
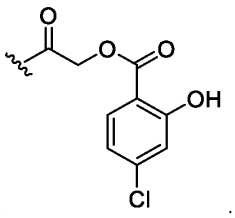
X^4 is independently selected, for each occurrence, from CH and N;

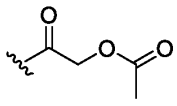
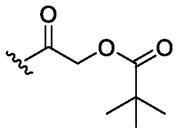
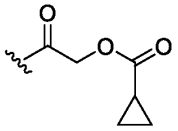
R^E is independently selected, for each occurrence, from the group consisting of halogen, -CN, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -OCH_3, -CF_3, -OCF_3 and -SCF_3; and

p is selected from 0, 1 and 2.

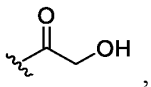
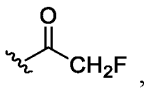
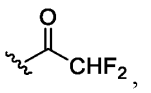
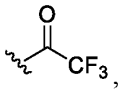
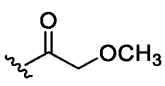
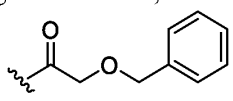
11. R^D is selected from the group consisting of  ,  ,  and  .

12. A is selected from the group consisting of  ,  ,  ,  ,  ,  .

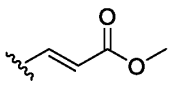
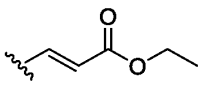

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,

,

and

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13. A is selected from the group consisting of  ,  and  .

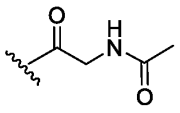
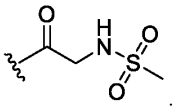
14. A is –C(O)R^D, wherein R^D is selected from the group consisting of hydrogen, $–CH_2OH$, $-CH_2OR'$ and $–CH_xF_y$, wherein R' is selected from the group consisting of C_1-C_8alkyl, -(C_1-C_8alkyl)-(5-10 membered aryl), C_1-C_8heteroalkyl, C_3-C_6cycloalkyl and 5-10 membered aryl, wherein x is 0, 1 or 2; y is 1, 2 or 3; and the sum of x and y is 3.

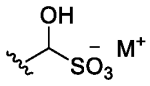
15. A is selected from the group consisting of  ,  ,  ,  ,  ,  and  .

16. A is –(CH=CH)C(O)OR^D, wherein R^D is C_1-C_8alkyl.

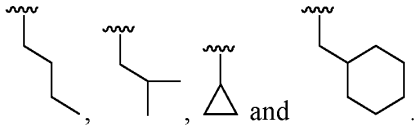
17. A is selected from  and  .

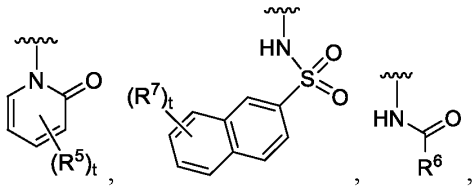
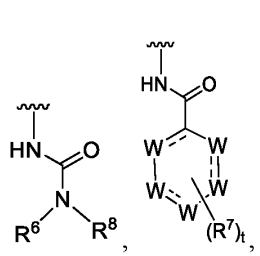
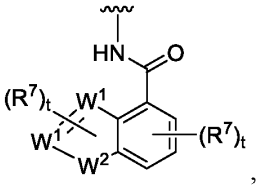
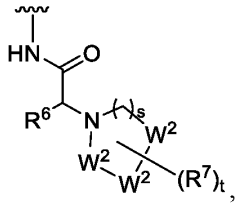
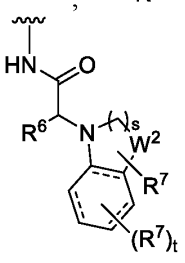
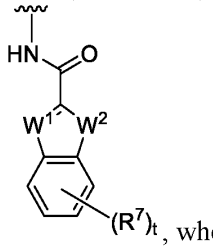
18. A is–$C(O)CH_2N(R^bR^c)$.

19. A is a warhead selected from  and  .

20. A is  , wherein M is selected from Na and K.

21. A is cyano.

22. R^1 is selected from the group consisting of  .

23. R^2 is selected from the group consisting of  , , ,  ,  ,  ,  ,  , and , wherein

$=\!=\!=\!=\!=\!=\!=$ denotes a bond that may be a single or double bond;

R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^6 is C_1-C_8alkyl;

R^7 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

R^8 is selected from the group consisting of 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

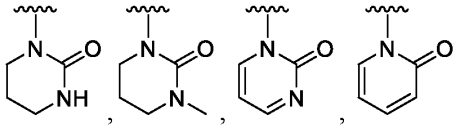
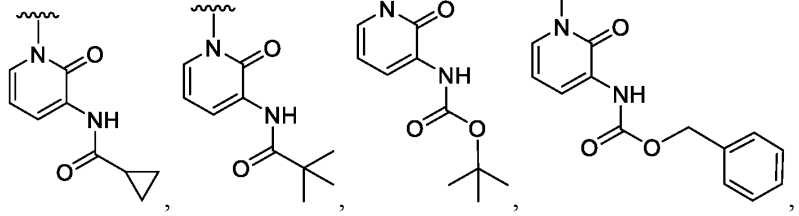
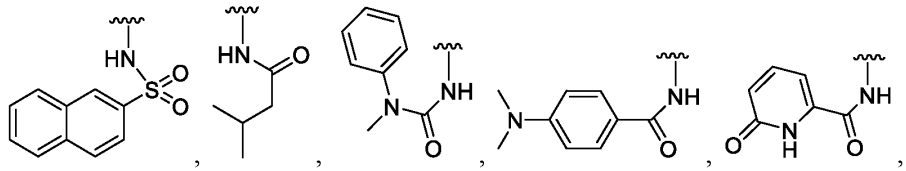
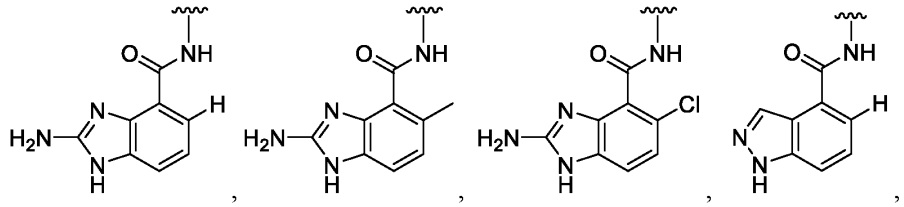
W^1 is selected from CH and N;

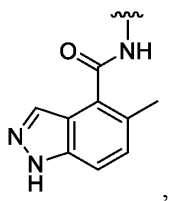
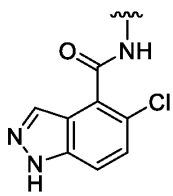
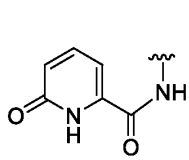
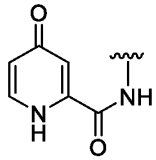
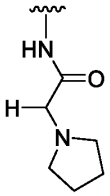
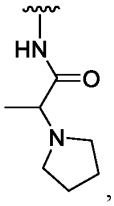
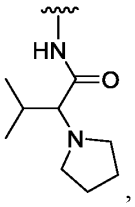
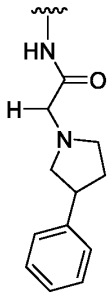
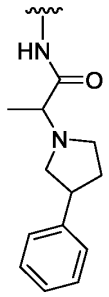
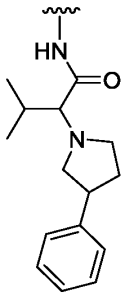
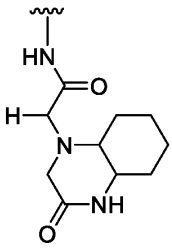
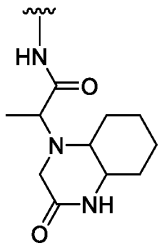
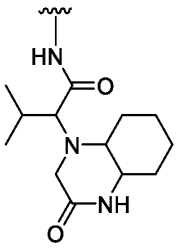
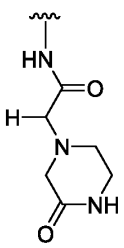
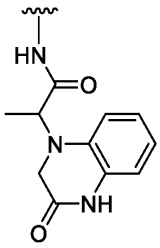
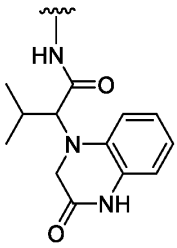
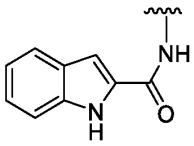
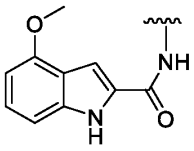
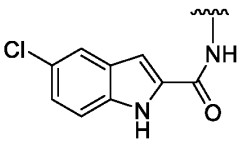
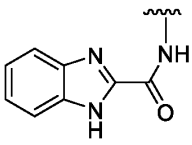
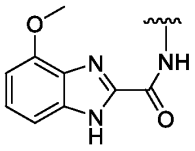
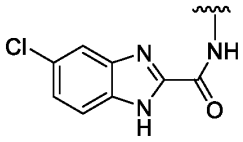
W^2 is selected from the group consisting of CH_2, O, NH and S;

W is selected from W^1 and W^2;

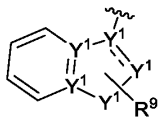
s is selected from 1 and 2; and

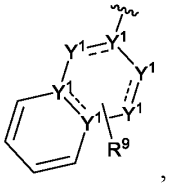
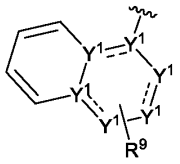
t is selected from 0, 1, 2 and 3.

24. R^2 is selected from the group consisting of  ,  ,  , 






















and


25. R^3 is selected from the group consisting of



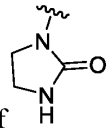
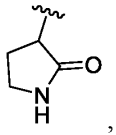
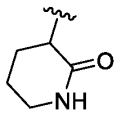
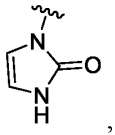
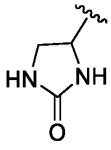
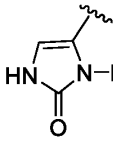
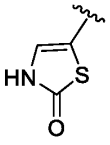
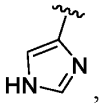
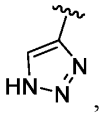
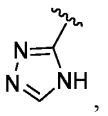
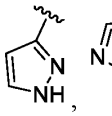
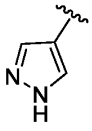
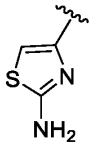
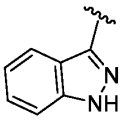
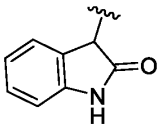
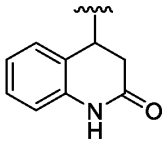
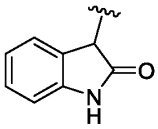
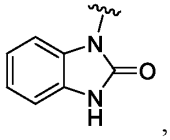
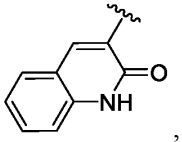
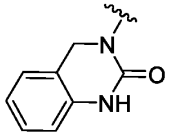
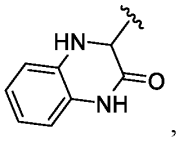
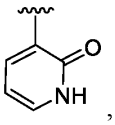
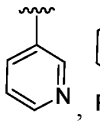
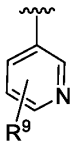
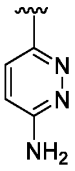



wherein

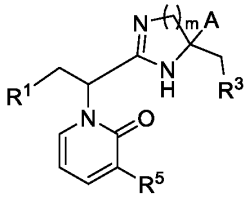
======= denotes a bond that may be a single or double bond;

Y^1 is selected from the group consisting of CH, CH_2, N, NH, O and S;

R^9 is selected from the group consisting of halogen, hydroxyl, oxo, $–NH_2$, $–N(CH_3)_2$, $–N(CH_2CH_3)_2$, $–CH_3$, $–CH_2CH_3$, $–OCH_3$ and $–OCH_2CH_3$.

26. R^3 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

27. The compound is represented by



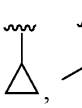
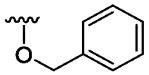
Formula I-A,

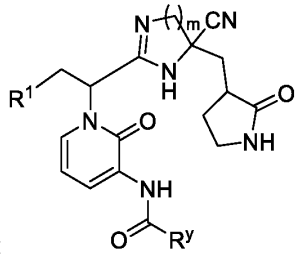
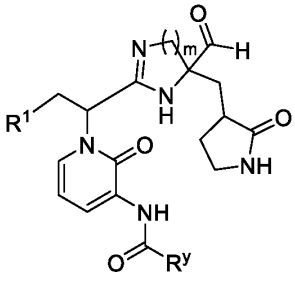
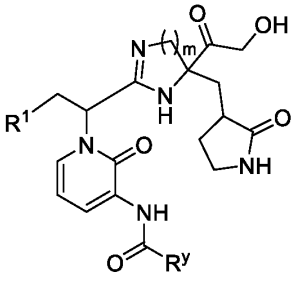
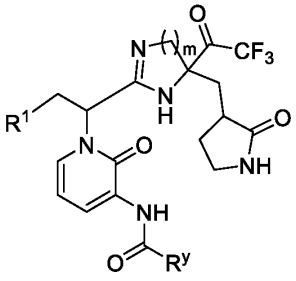
wherein:

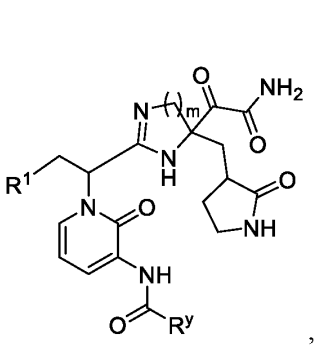
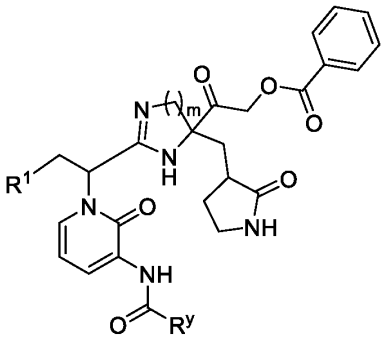
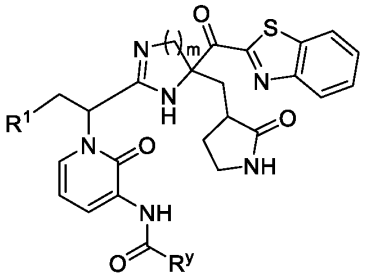
R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl; and

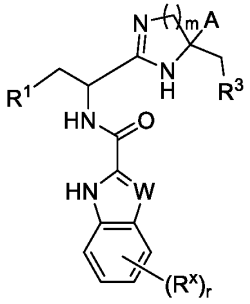
m is selected from 1 and 2.

28. R^y is selected from the group consisting of hydrogen,  ,  ,  and  .

29. The compound is selected from the group consisting of:  ,  ,  ,  ,



, and


30. The compound is represented by



Formula I-B,

wherein

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

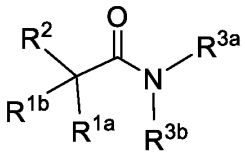
W is CH or N;

m is selected from 1 and 2; and

r is selected from 0, 1, 2 and 3.

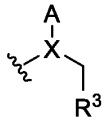
31. R^x is $-OCH_3$.

32. A protease inhibitor compound represented by:



Formula II,

wherein



R^{3a} is selected from and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of C_1-C_8alkyl, $-(C_1$-C_8alkyl)-R^1, $-(C_1$-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–NH_2$, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocycle), –C(O)-O-(4-10 membered heterocycle), $–C(O)-OC(CH_3)_3$, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl) C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the heterocycle, heteroaryl, or aryl may optionally be substituted by one, two or three substituents of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl or oxo;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, SF_5, cyano, $–C(O)O(CH_3)$, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

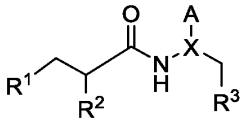
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $–(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a warhead;

X is selected from CH, $C(CH_3)$ and N; and

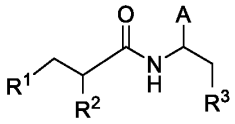
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

33. The compound is represented by:



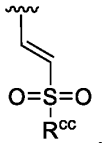
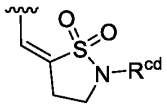
Formula II-A.

34. The compound is represented by:



Formula II-B.

35. A is selected from the group consisting of cyano, $–C(O)R^D$, $–C(O)CH_2N(R^bR^c)$, $–C(O)CH_2OC(O)R^D$, $–C(O)C(O)R^D$, $–(CH=CH)C(O)OR^D$, $–(CH=CCN)C(O)OR^D$, –

(CH=CCN)C(O)(NH)R^D, –CH(CN)(OH), -CH(CN)(NR^{b}R^c),  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} –N(R^{b}R^c), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

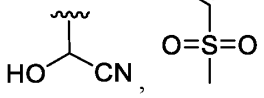
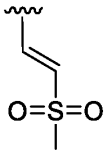
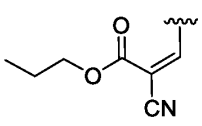
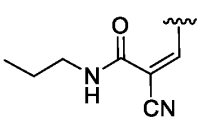
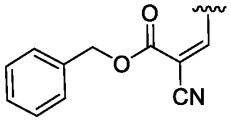
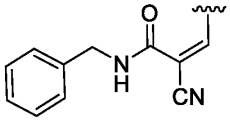
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

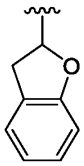
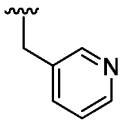
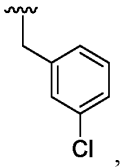
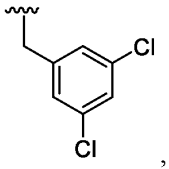
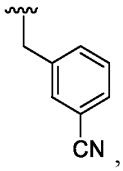
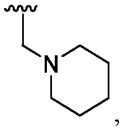
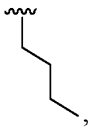
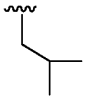
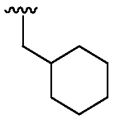
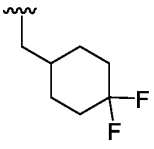
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^{b}R^c), wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

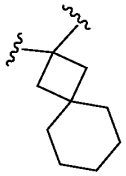
R^b and R^c are each selected from the group consisting of hydrogen, –CH_2C(O)O(C_1-C_8alkyl), –C(O)-(C_1-C_8alkyl), –S(O)$_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

36. A is selected from the group consisting of -CN,  ,  ,  ,  ,  , and  .

37. R^{1a} is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

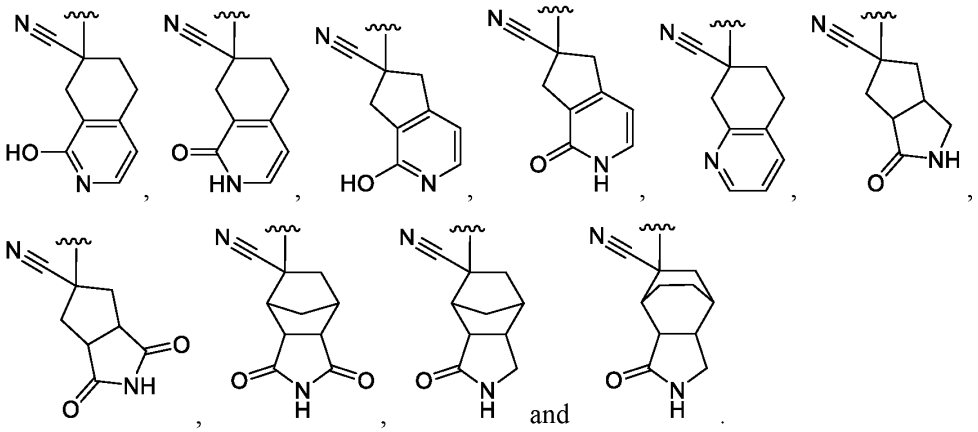
38. R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

39. R^{1b} is hydrogen.

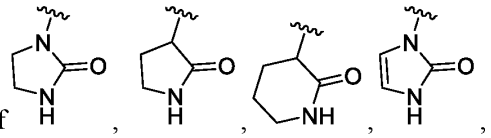
40. R^{1a} and R^{1b} are joined to together to form  .

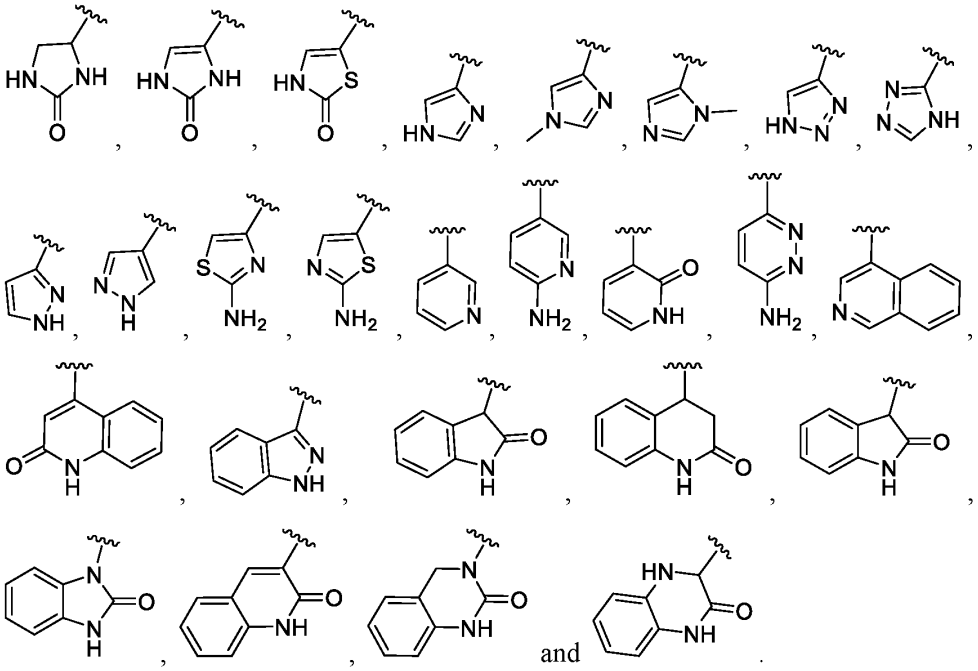
41. R^{3a} is a 4-10 membered heterocycle substituted by A.

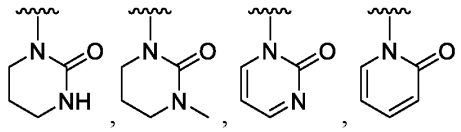
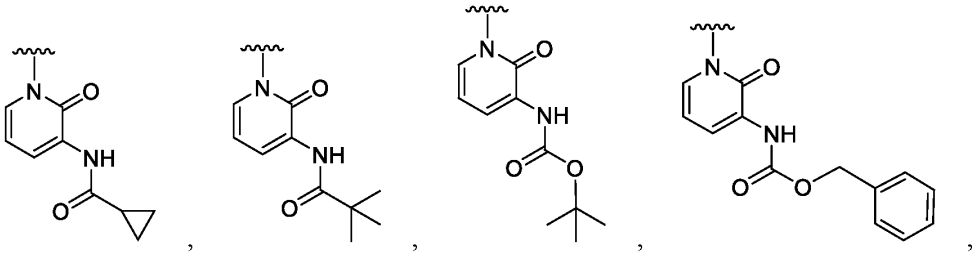
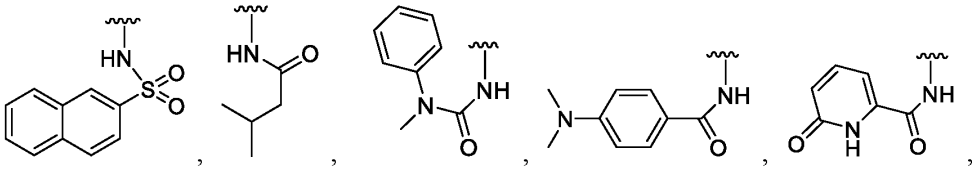
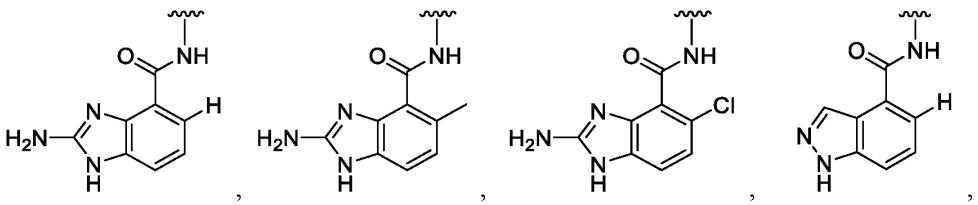
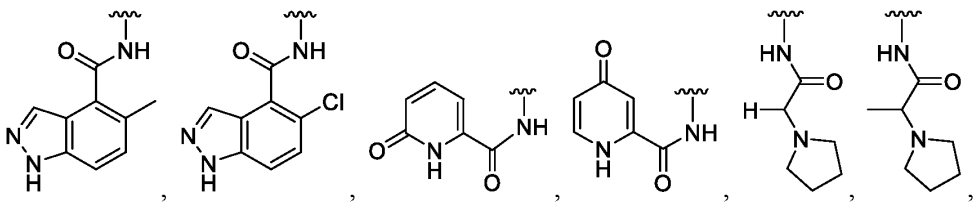
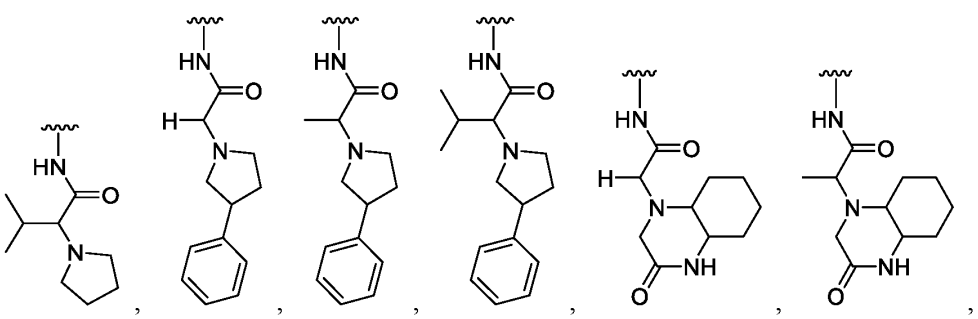
42. R^{3a} is selected from the group consisting of

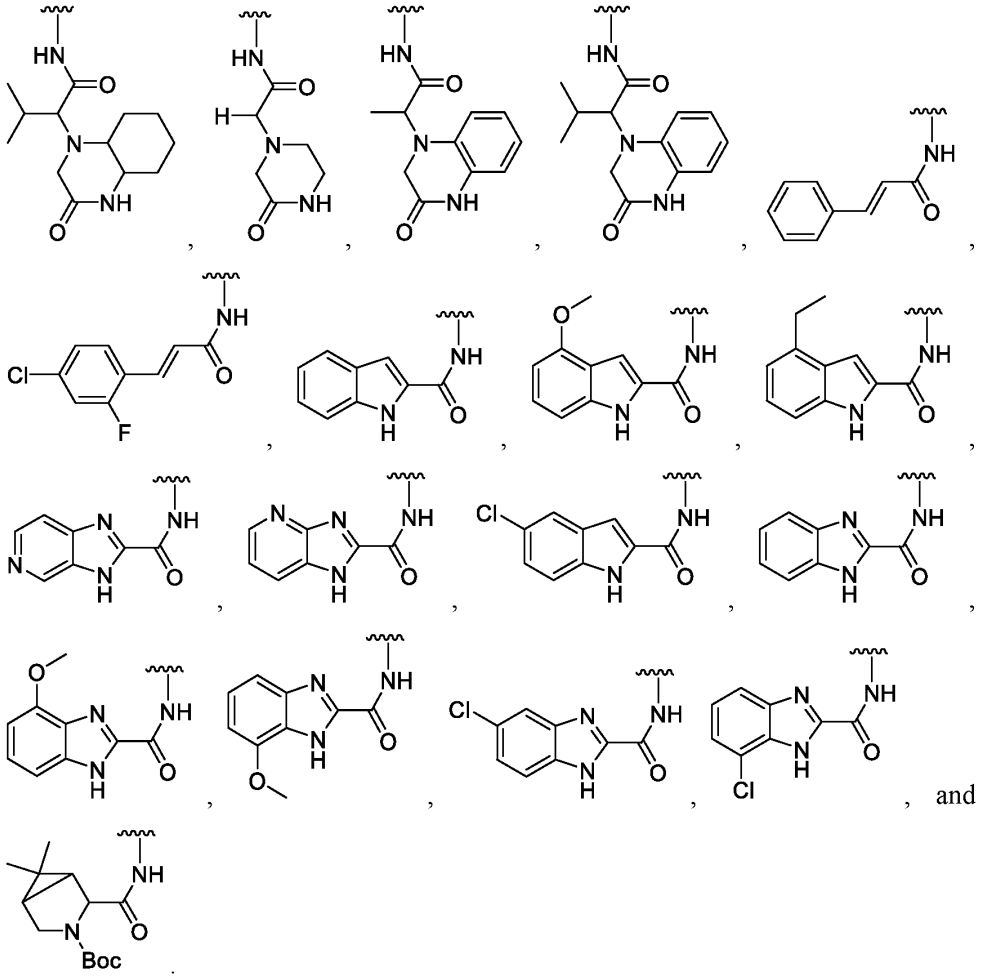


43. R^3 is a 4-10 membered heterocycle.

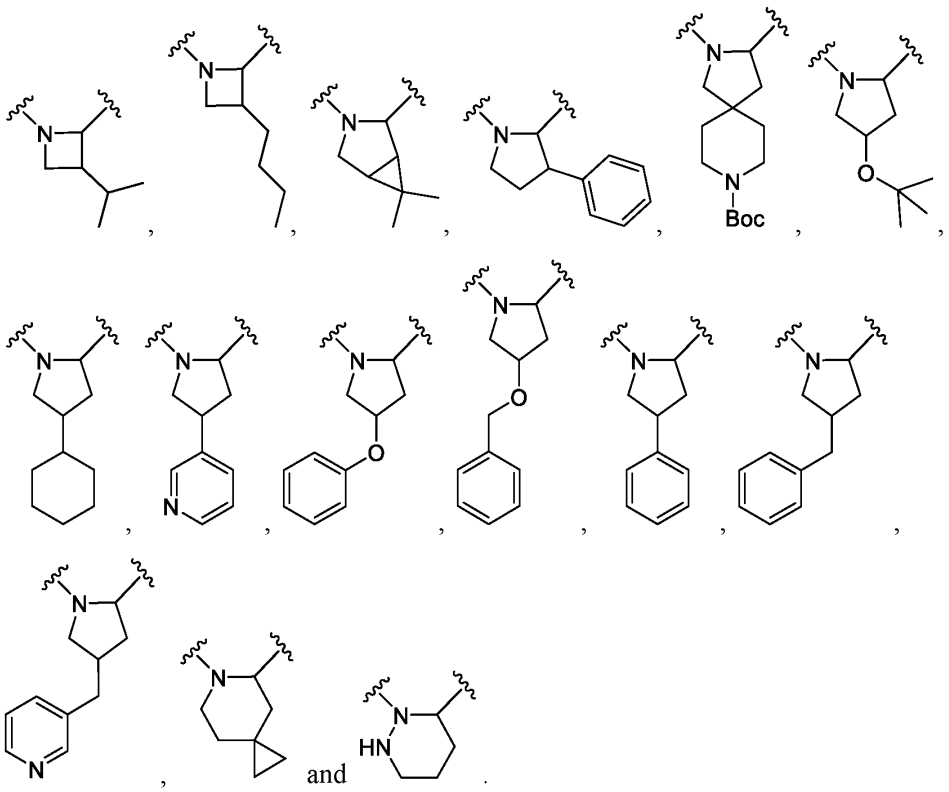
44. R^3 is selected from the group consisting of 



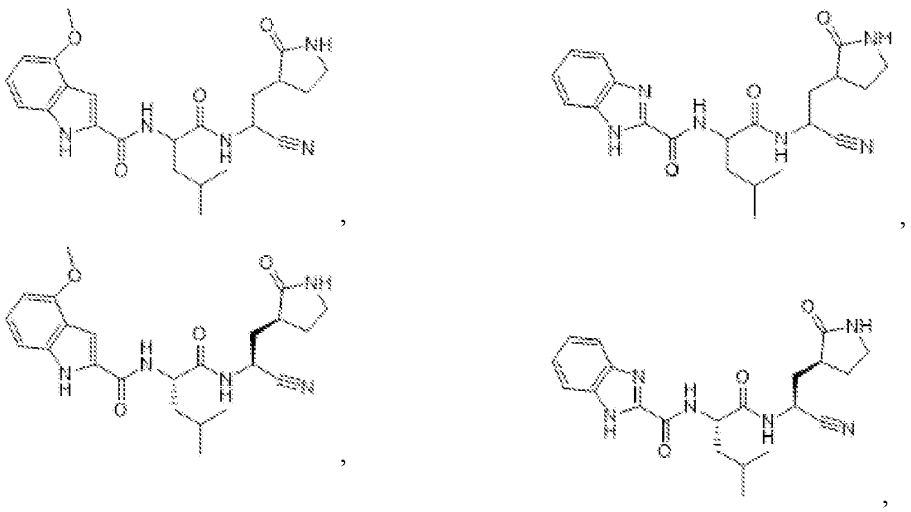
45. R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,

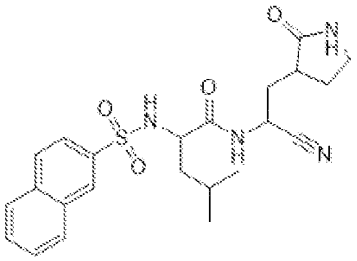


46. R^{1a} and R^2 are joined to together to form the heterocycle selected from the group consisting of:

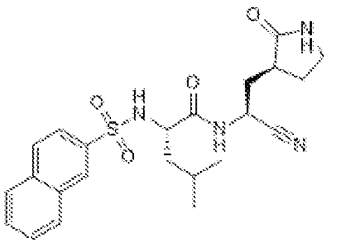


47. The compound is selected from the group consisting of:

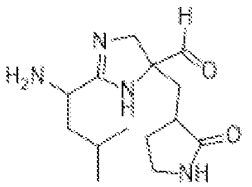




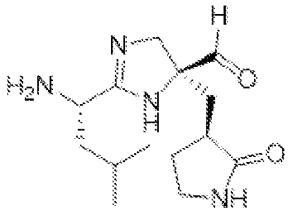
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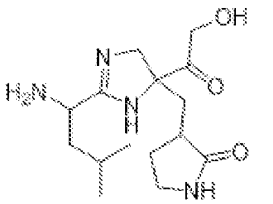
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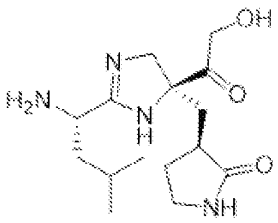
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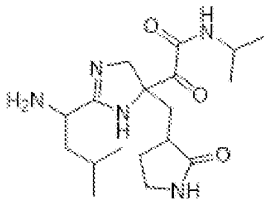
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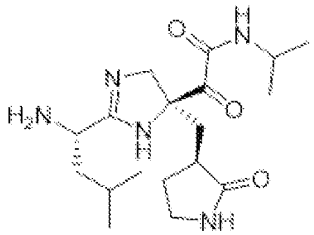
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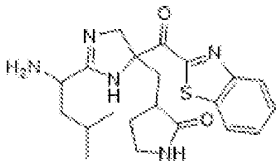
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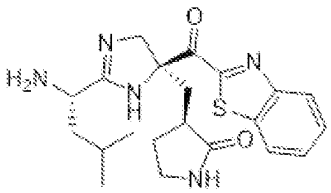
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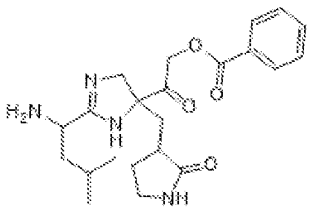
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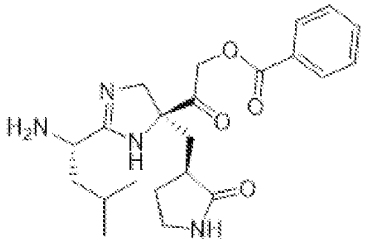
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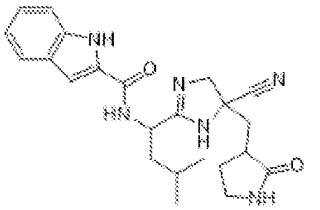
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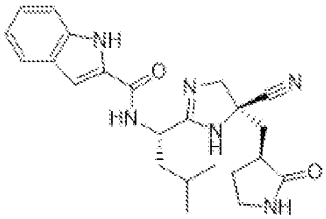


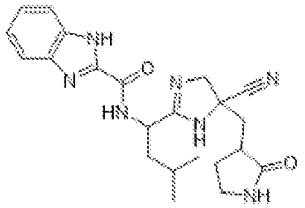
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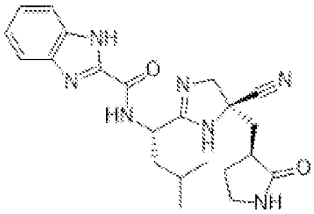


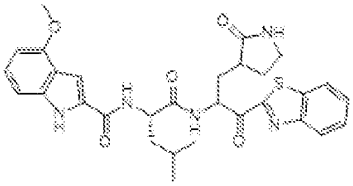
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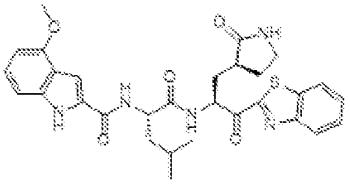

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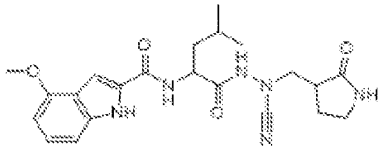

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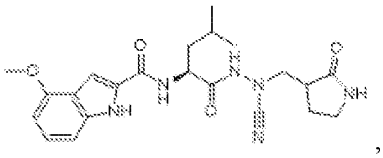

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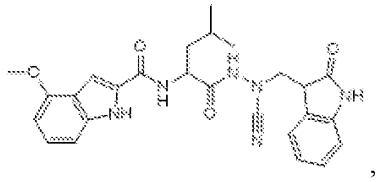

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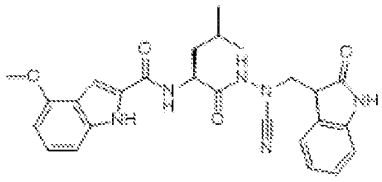

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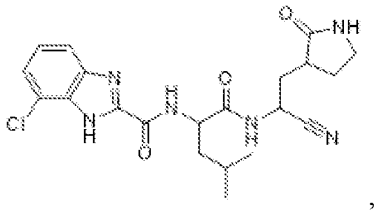

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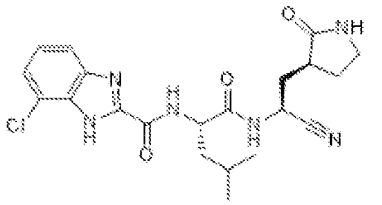

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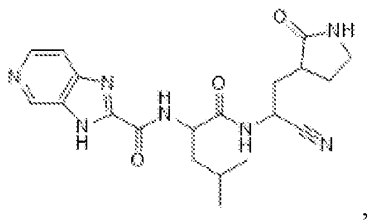

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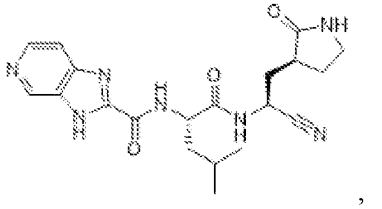

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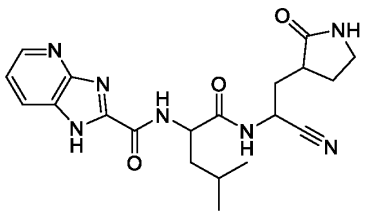

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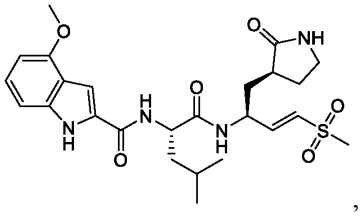

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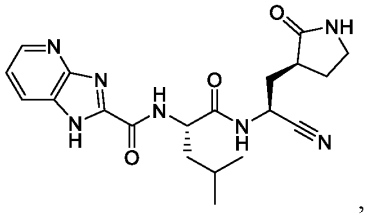

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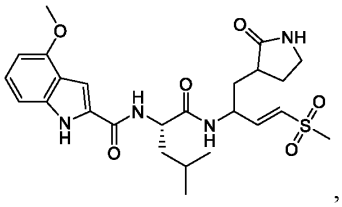
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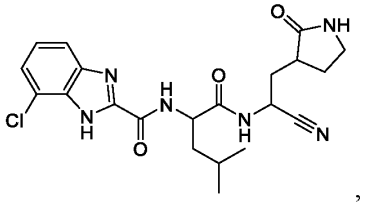
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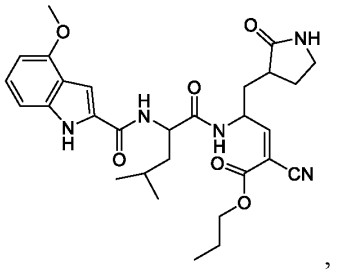
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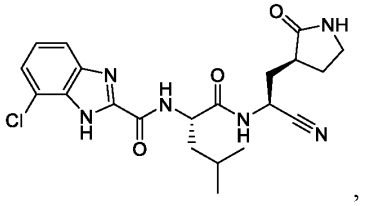
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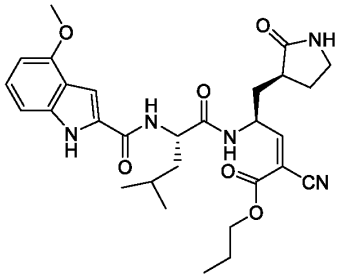
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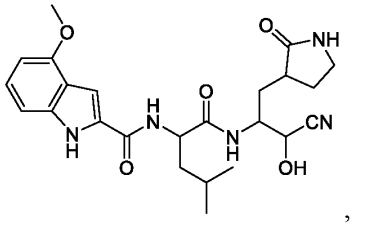
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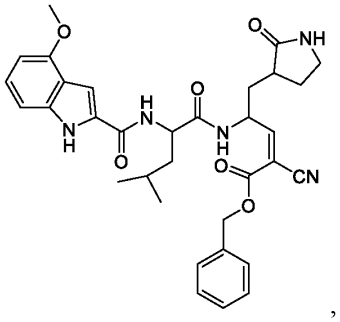
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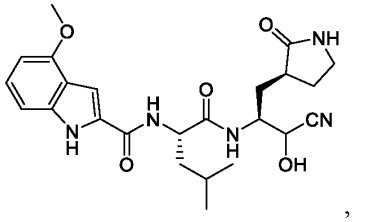
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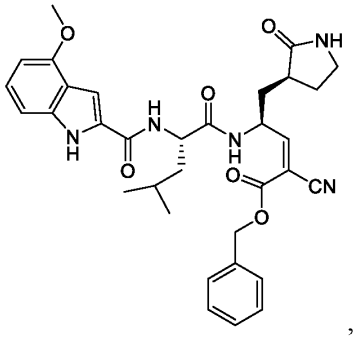
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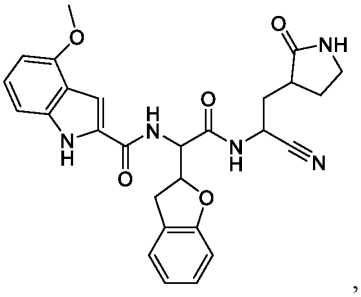
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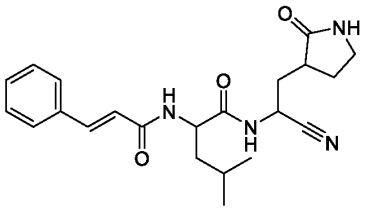
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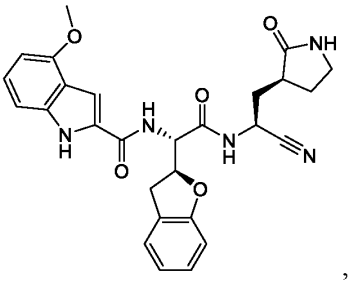
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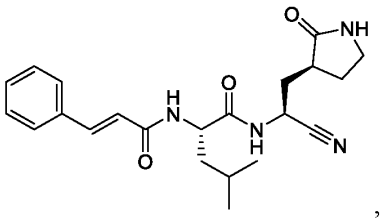
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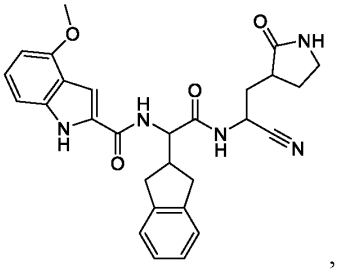
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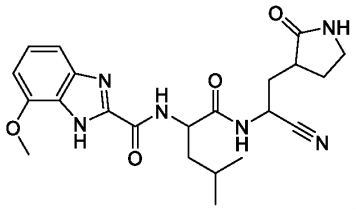
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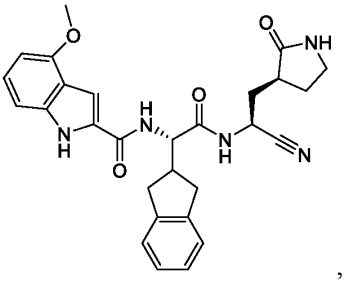
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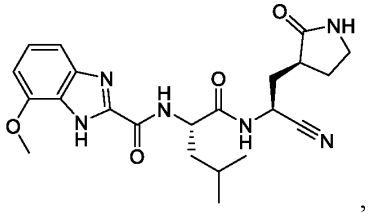
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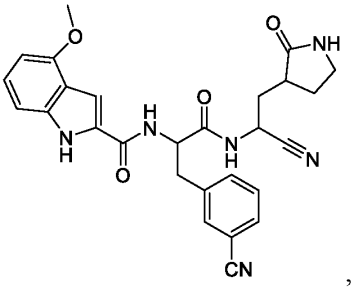
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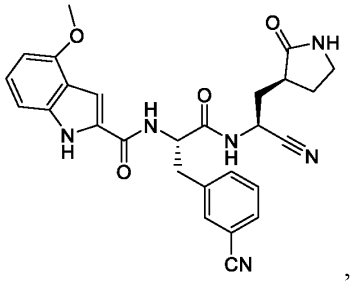
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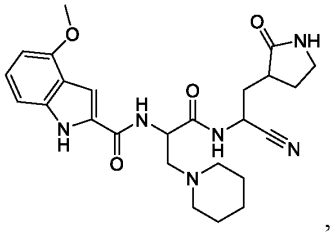
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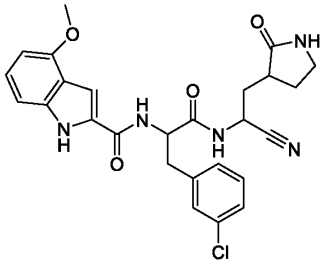
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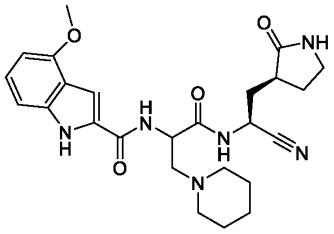
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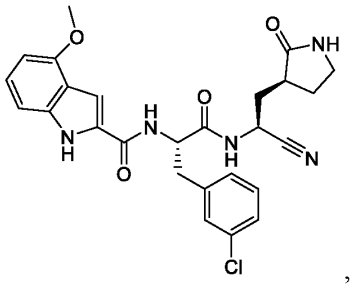
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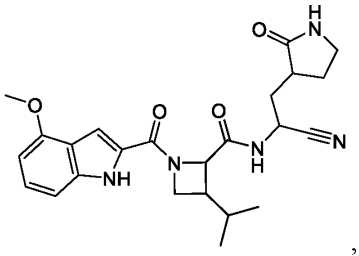
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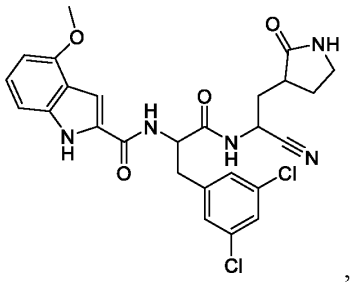
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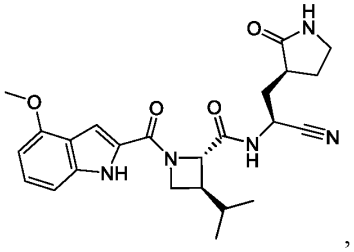
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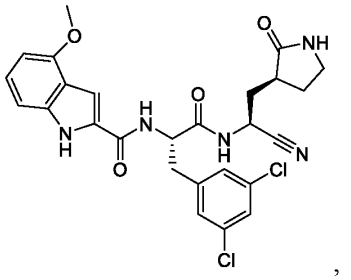
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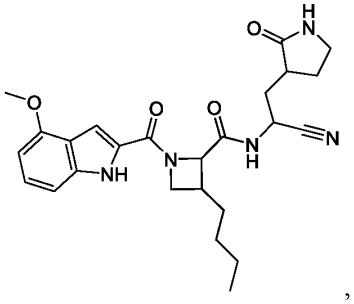
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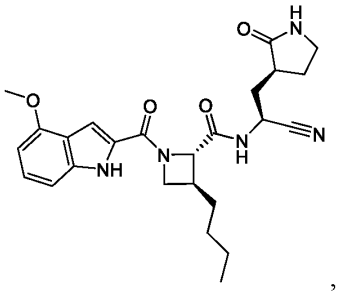
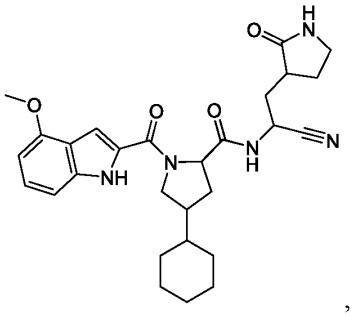
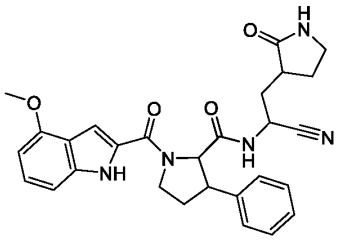
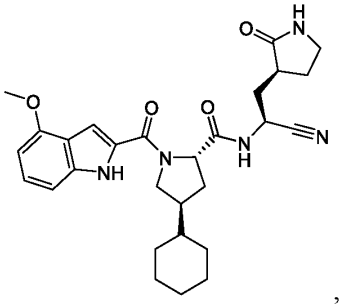
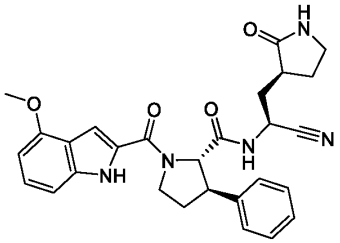
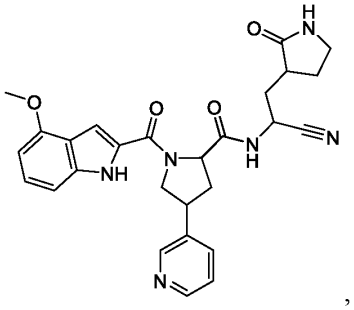
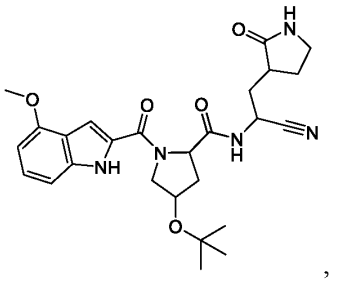
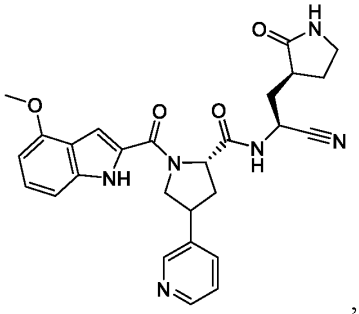
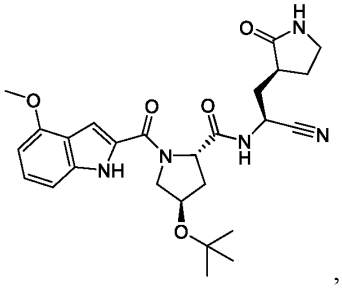


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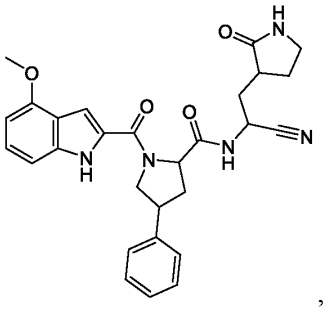
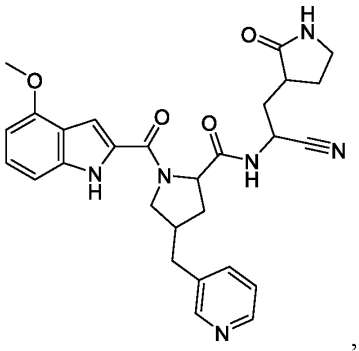
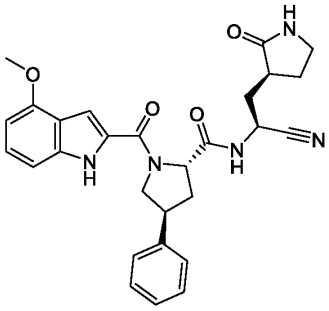
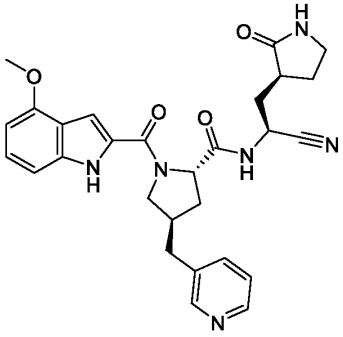
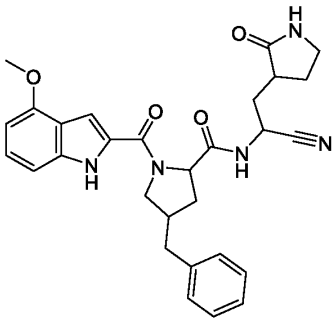
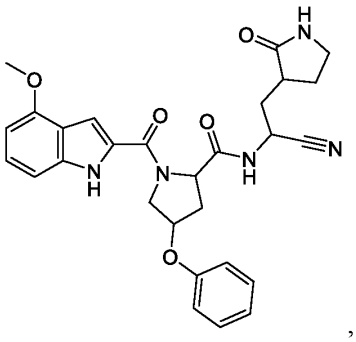
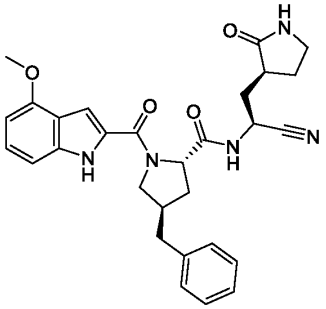
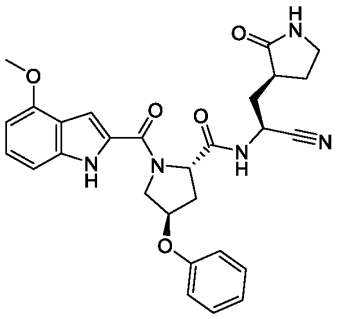


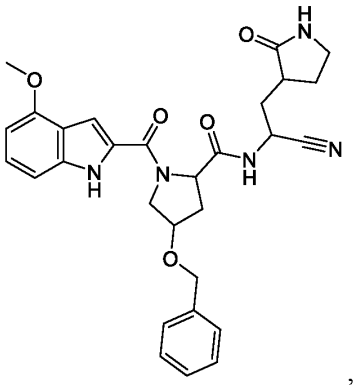
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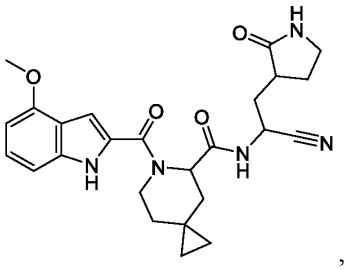

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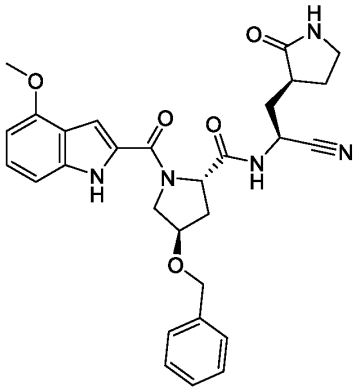

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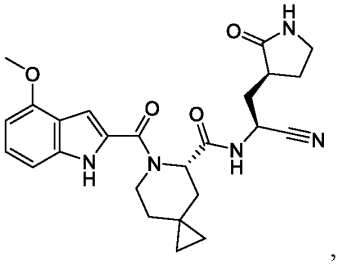
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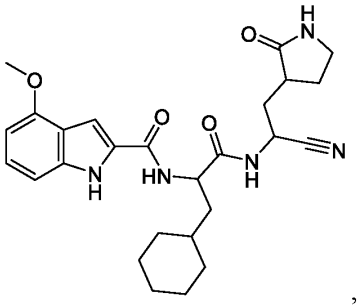
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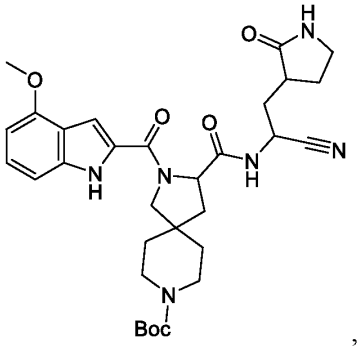
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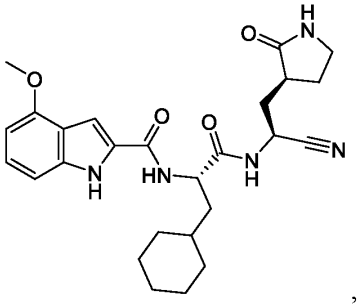
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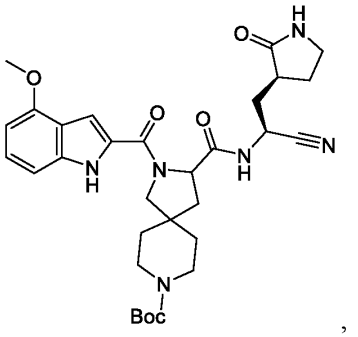
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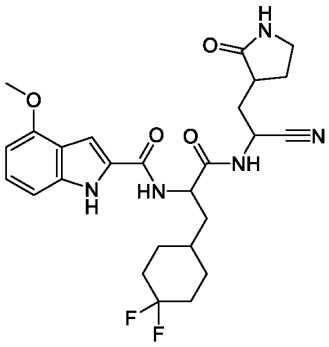
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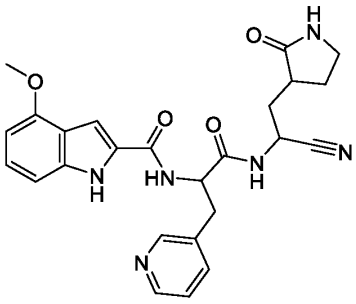
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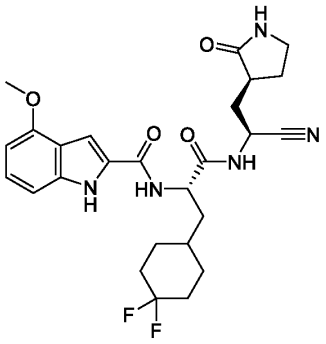
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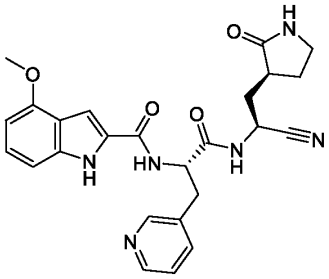
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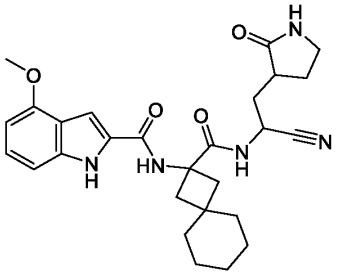
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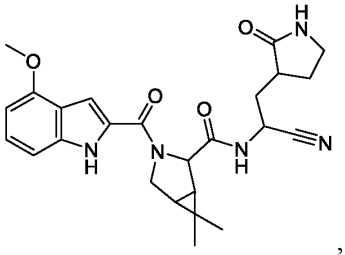
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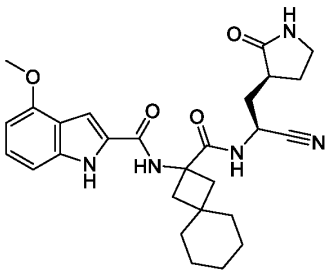
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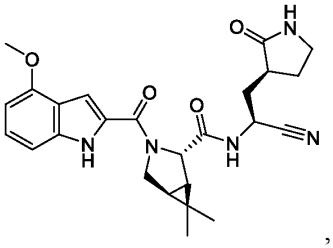
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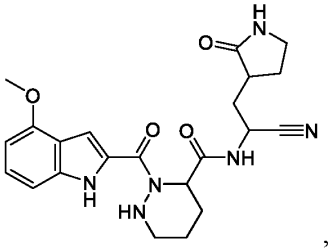
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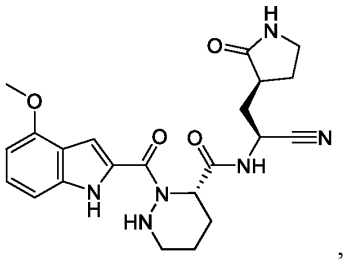
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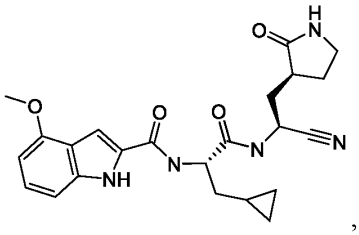
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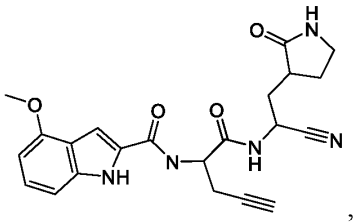
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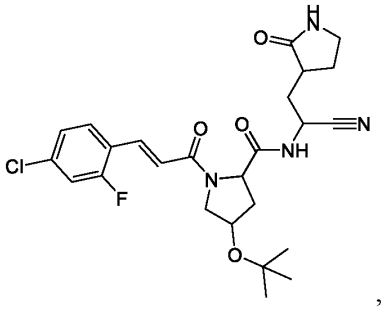
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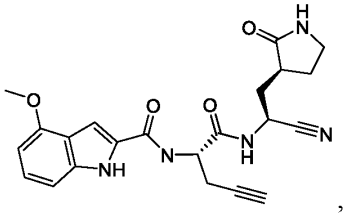
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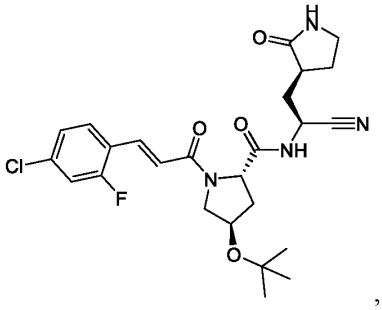
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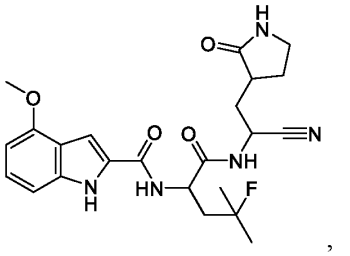
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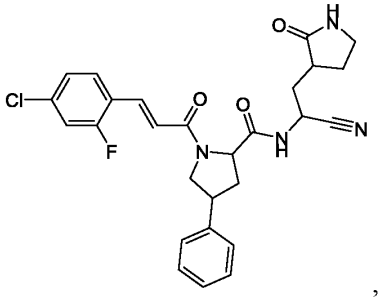
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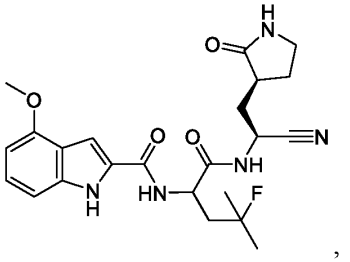
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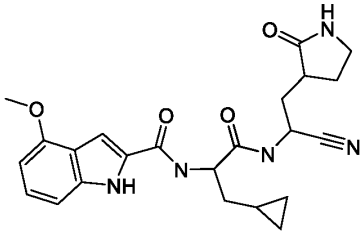
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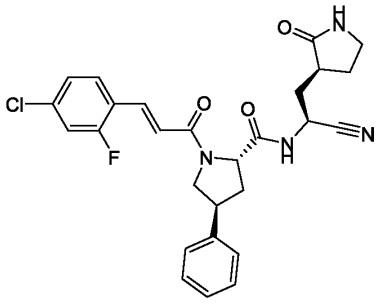
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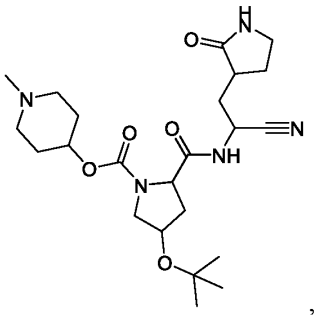


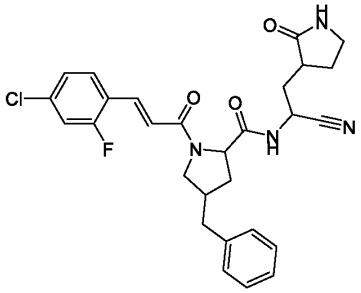
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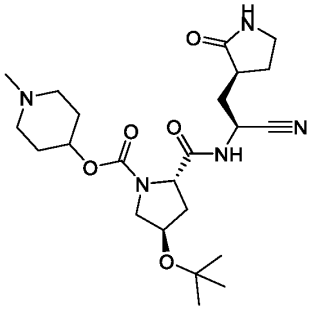


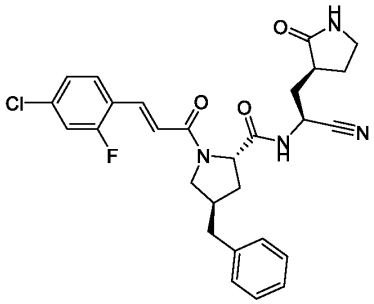
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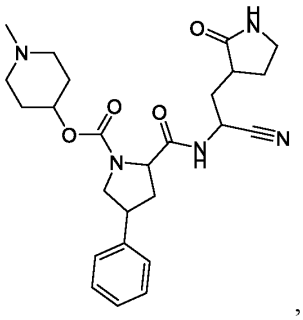

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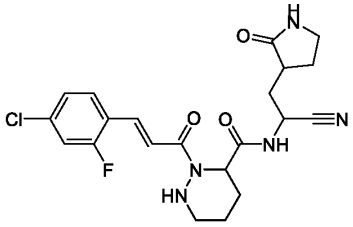

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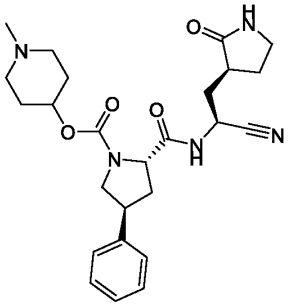

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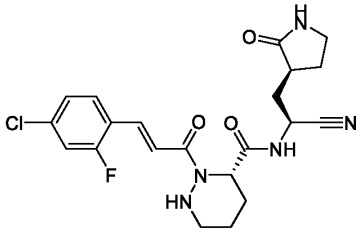

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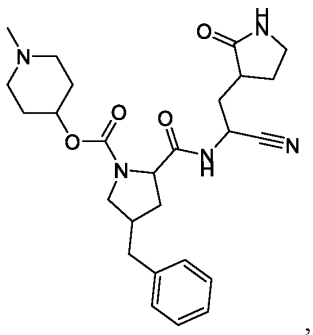

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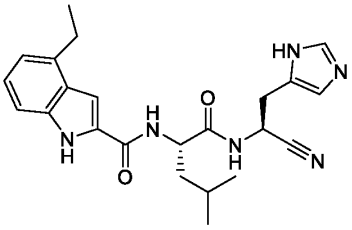

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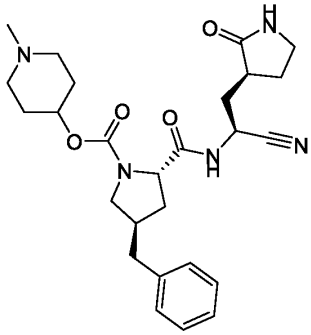

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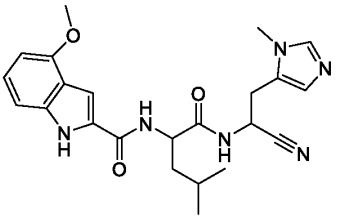
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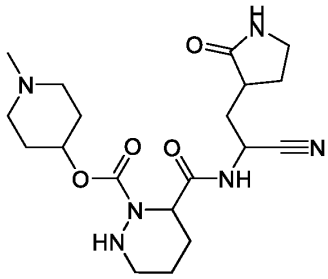
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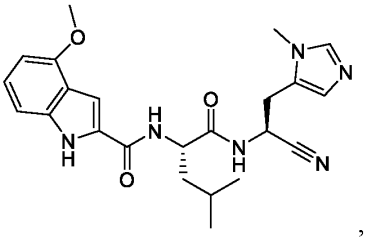
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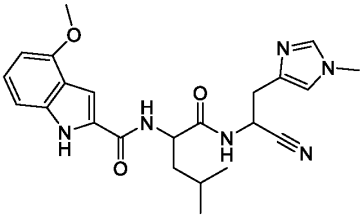
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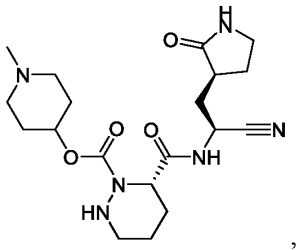
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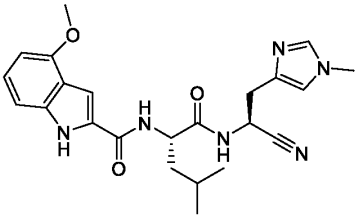
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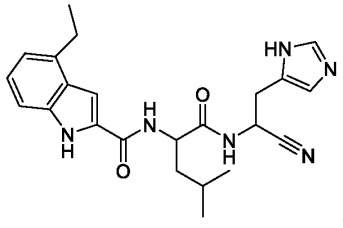
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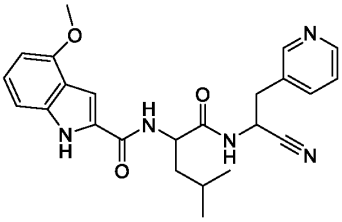
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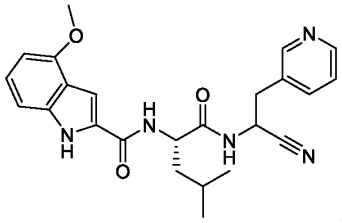
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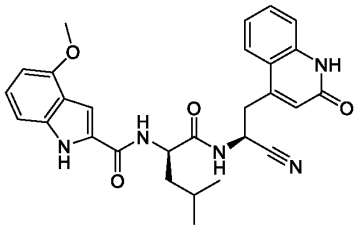
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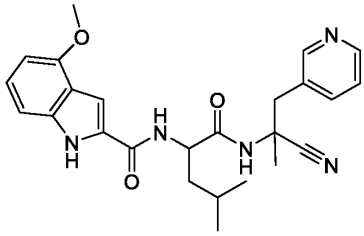
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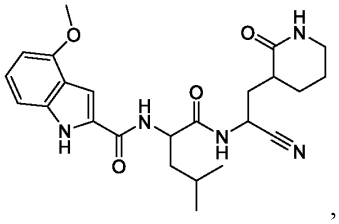
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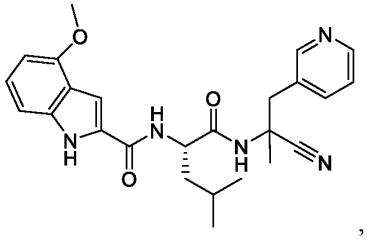
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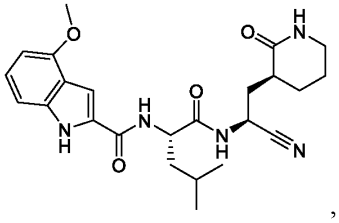
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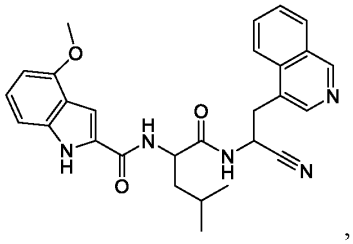
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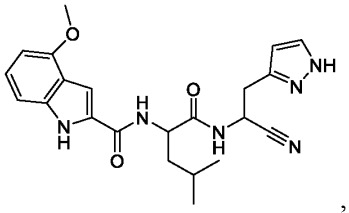
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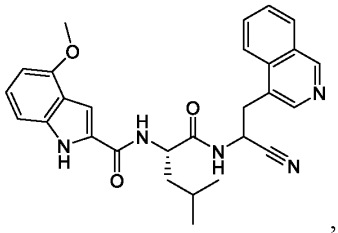
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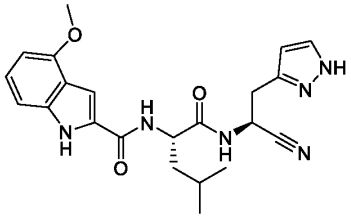
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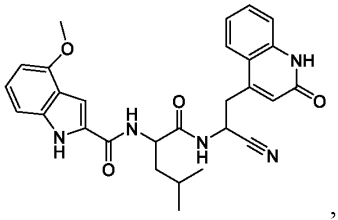
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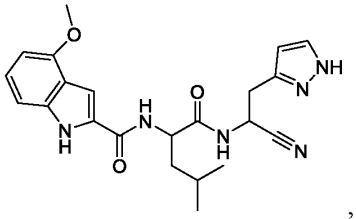
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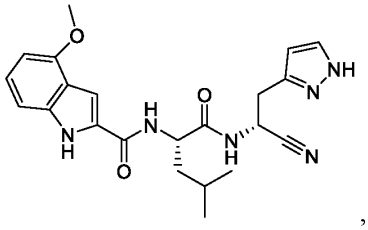
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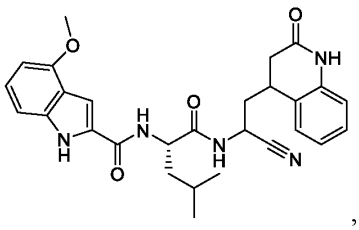
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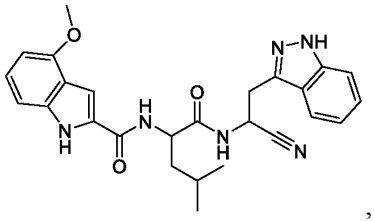
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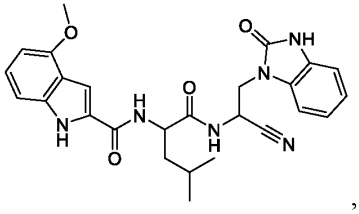
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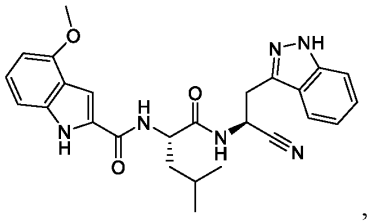
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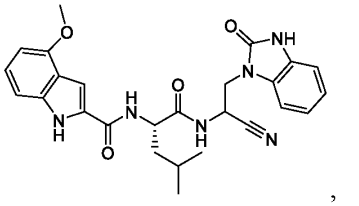
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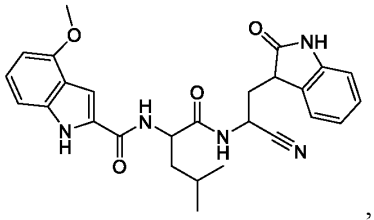
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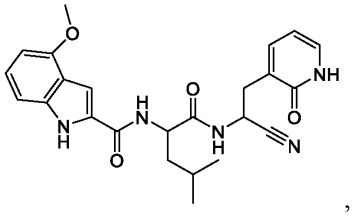
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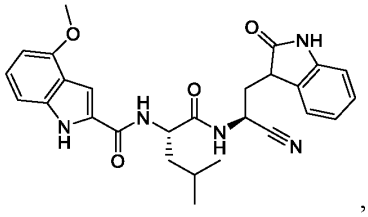
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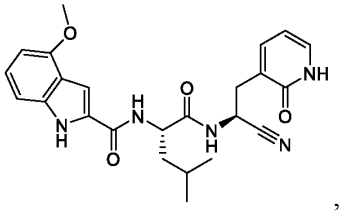
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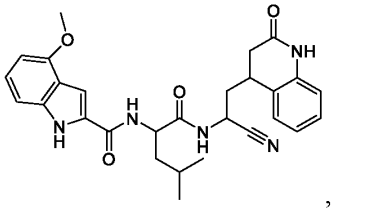
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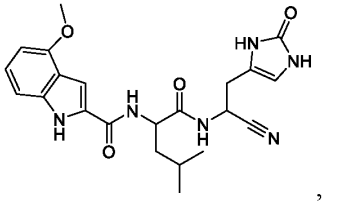
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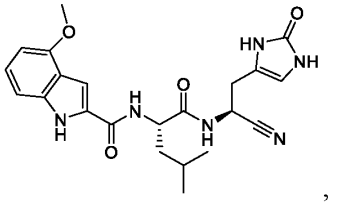


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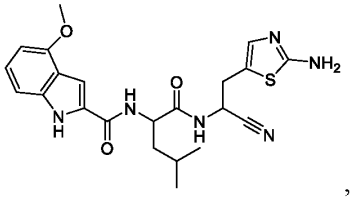


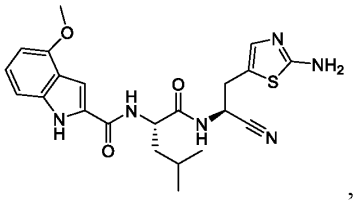
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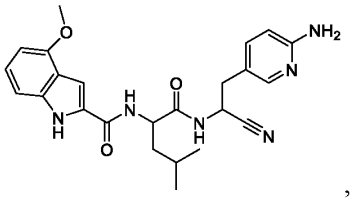
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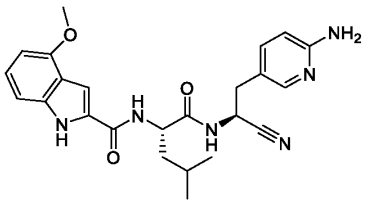


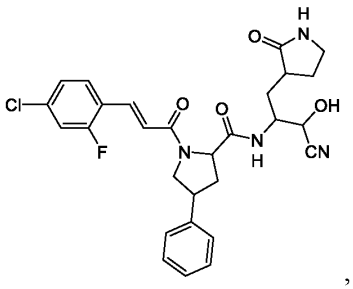
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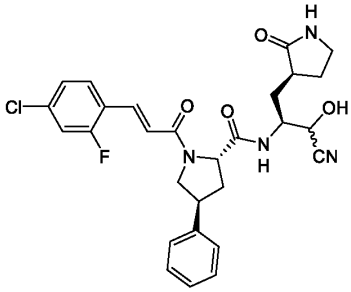

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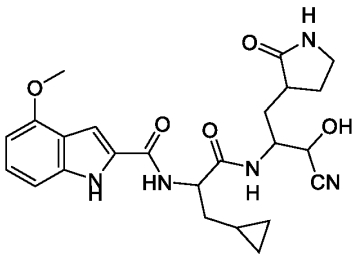

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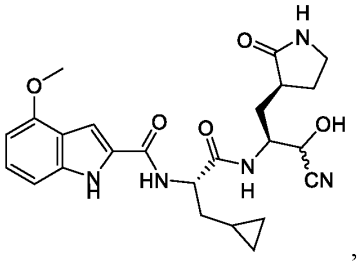

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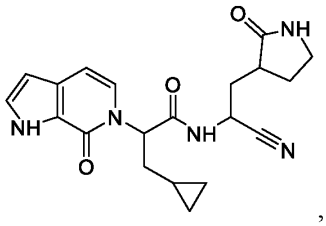

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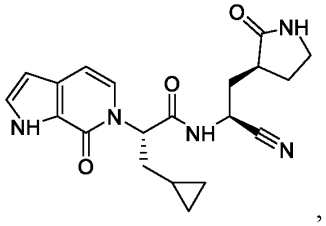

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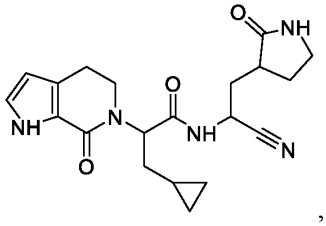

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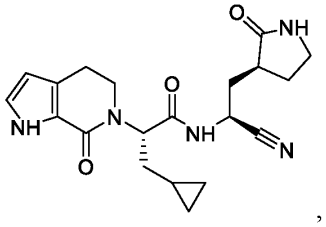

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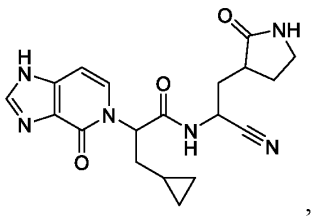

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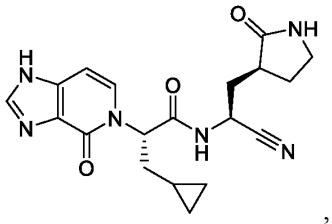

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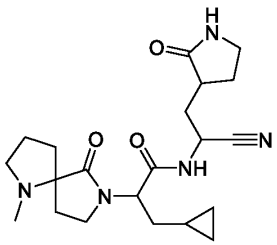

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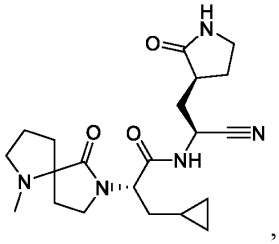
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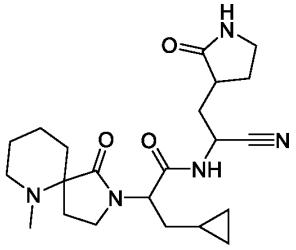
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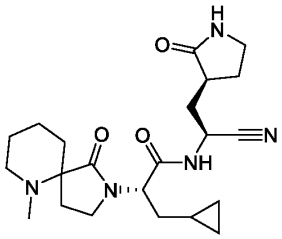
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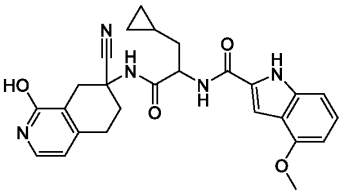
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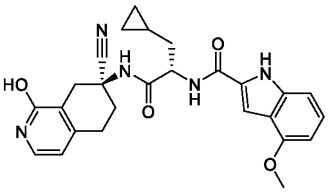
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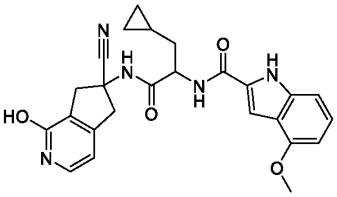
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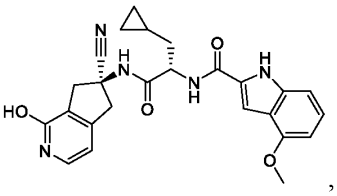
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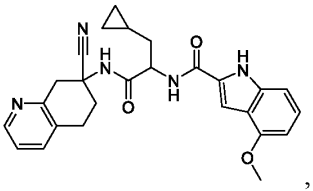
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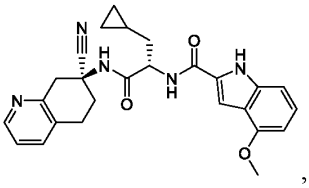
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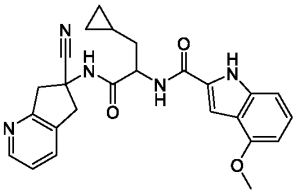
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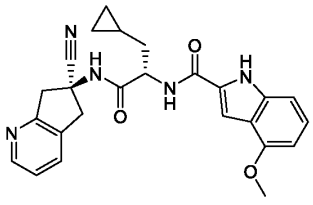
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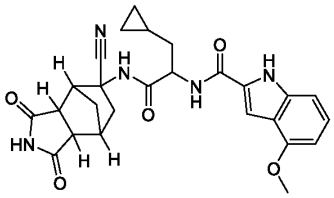
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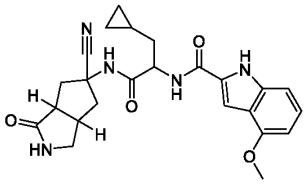
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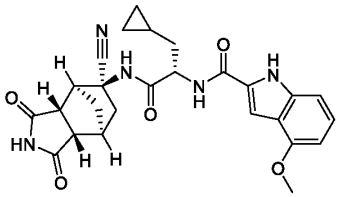
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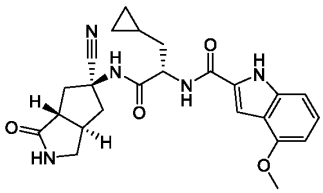
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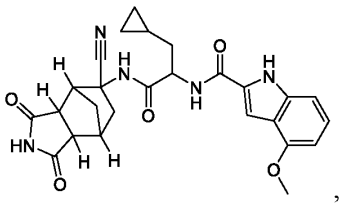
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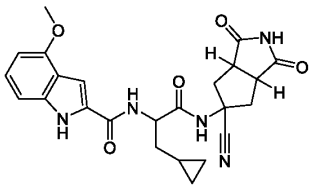
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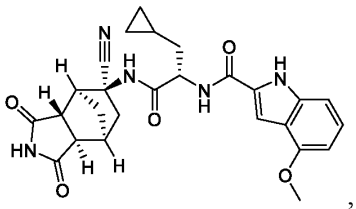
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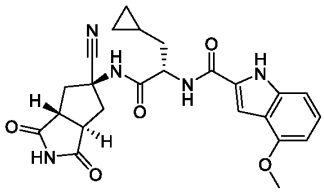
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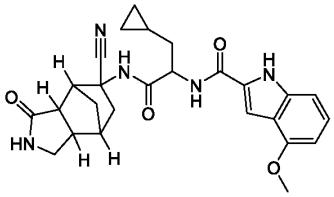
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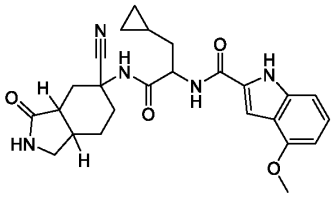
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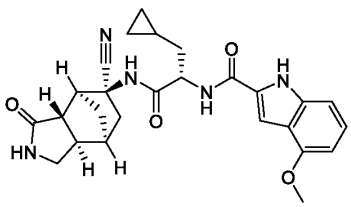
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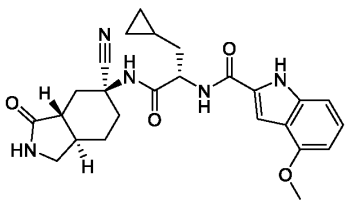
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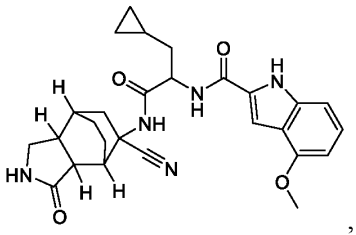
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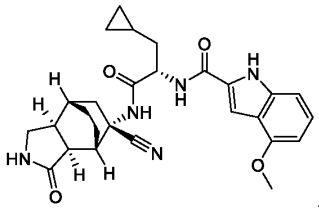
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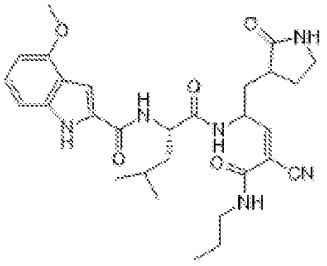


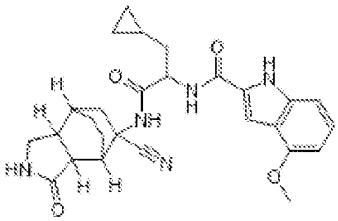
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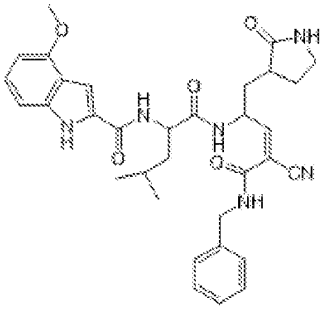


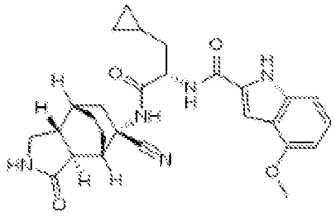
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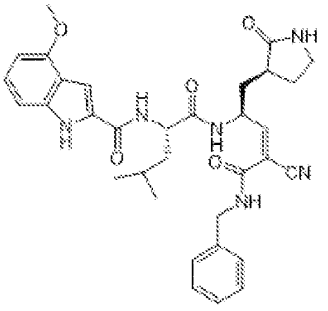

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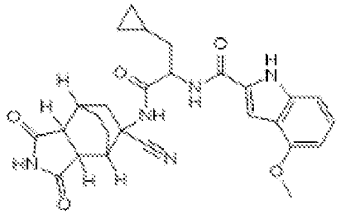

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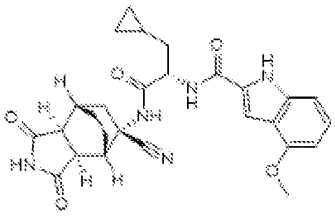

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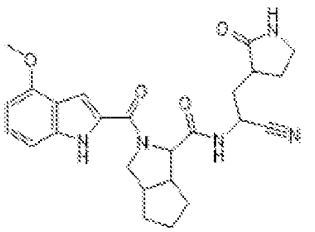

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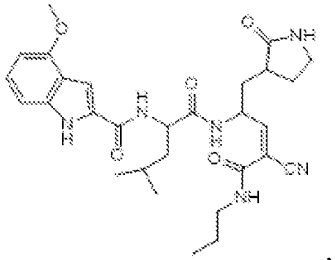

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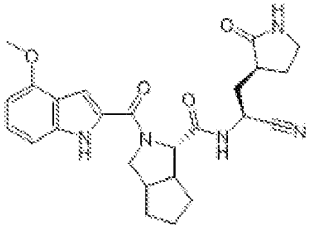

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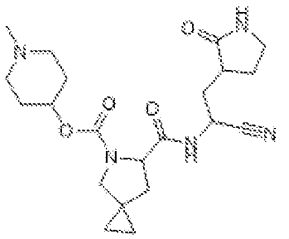

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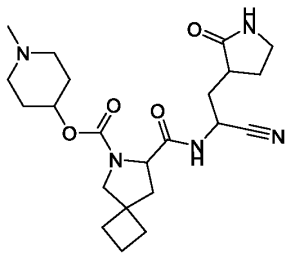

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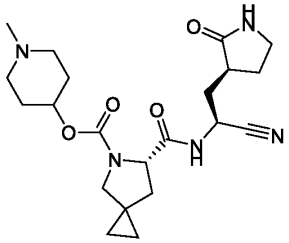

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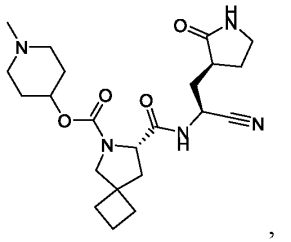

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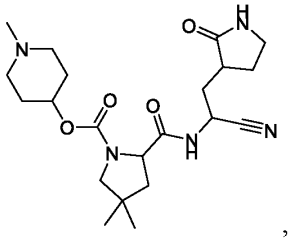

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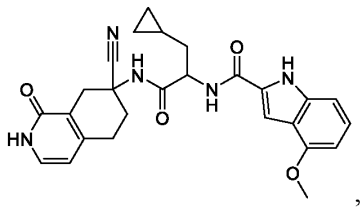

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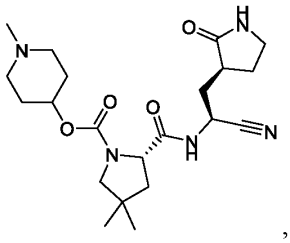

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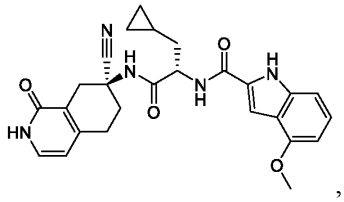

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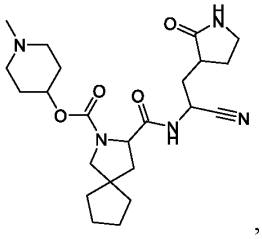

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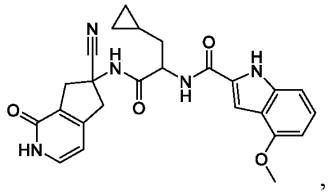

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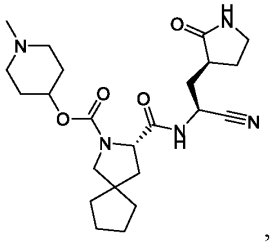

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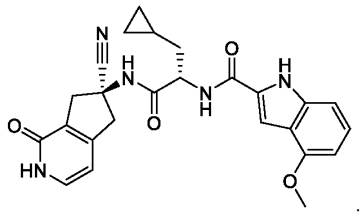

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48. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds of the embodiment.

49. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
50. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.
51. The viral infection is a coronavirus infection.
52. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).
53. The viral infection is SARS-CoV-2.
54. The viral infection is an arenavirus infection.
55. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.
56. The viral infection is an influenza infection.

57. The influenza is influenza H1N1, H3N2 or H5N1.
58. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of any compound

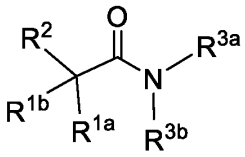
of the embodiment to a patient suffering from the virus, and/or contacting an effective amount of any compound of the embodiment with a virally infected cell.

59. The method further comprises administering another therapeutic.
60. The method further comprises administering an additional anti-viral therapeutic.
61. The anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, and remdesivir.
62. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.
63. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, and remdesivir.
64. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of any compound of the embodiment.
65. The compound is administered before viral exposure.
66. The compound is administered after viral exposure.

4. Contemplated Embodiment

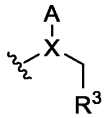
[000193] In another aspect, the compositions, compounds and methods of the present disclosure may be described in another embodiment as follows:

1. A protease inhibitor compound represented by:



Formula II,

wherein:

R^{3a} is selected from  and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, –CH_2CF_3, CF_3, –O-CF_3, –O-CHF_2, –S-CH_3, –$S(O)_2$-CH_3, –NH_2, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –$NHC(O)R^B$, –$NHC(O)OR^B$, –NHC(O)O-(C_1-C_8alkyl)-R^B, –$N(R^y)_2$, –$N(R^y)$(C_1-C_8alkyl)C(O)O-phenyl, –$N(R^y)$(C_1-C_8alkyl)$C(O)N(R^y)_2$, –

$NHC(O)O(C_1\text{-}C_8alkyl)R^B$, –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocycle), –C(O)-O-(4-10 membered heterocycle), $–C(O)\text{-}OC(CH_3)_3$, $–C(O)\text{-}(C_2\text{-}C_{10}alkenyl)\text{-}(C_6\text{-}C_{14}aryl)$, $C_1\text{-}C_8alkyl$, $C_2\text{-}C_{10}alkenyl$, $C_2\text{-}C_{10}alkynyl$, $C_1\text{-}C_8heteroalkyl$, $C_1\text{-}C_8alkoxy$, $C_3\text{-}C_{10}cycloalkyl$, $–(C_1\text{-}C_8alkyl)\text{-}(C_3\text{-}C_{10}cycloalkyl)$, $–(C_1\text{-}C_8alkyl)\text{-}(C_6\text{-}C_{14}aryl)$, $–(C_1\text{-}C_8alkyl)$-(5-10 membered heteroaryl), $C_6\text{-}C_{14}aryl$, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the R^B, alkyl, heterocycle, heteroaryl, or aryl may optionally be substituted by one, two or three substituents of halogen, $C_1\text{-}C_8alkyl$, $C_1\text{-}C_8alkoxy$, SF_5, $–NH_2$, hydroxyl or oxo;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, $–O\text{-}(C_1\text{-}C_8alkyl)\text{-}(C_3\text{-}C_{10}cycloalkyl)$, 4-10 membered heterocycle, $C_6\text{-}C_{14}aryl$ and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a $C_3\text{-}C_{10}cycloalkyl$, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of $C_1\text{-}C_8alkyl$, $C_2\text{-}C_{10}alkenyl$, $C_2\text{-}C_{10}alkynyl$, $C_6\text{-}C_{14}aryl$, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and $C_1\text{-}C_8alkyl$;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, $–OCHF_2$, $–OCF_3$, $–O\text{-}(C_1\text{-}C_8alkyl)$, $–C(O)O(CH_3)$, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, $–N(R^y)(C_1\text{-}C_8alkyl)C(O)N(R^y)_2$, $–N(R^y)(C_1\text{-}C_8alkyl)C(O)OH$, $-(C_1\text{-}C_8alkyl)\text{-}(C_3\text{-}C_{10}cycloalkyl)$, $C_1\text{-}C_8alkyl$, $C_1\text{-}C_8alkoxy$, C_3-

C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo, halogen and C_1-C_8alkyl;

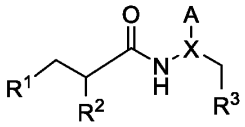
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, $–CH_2CF_3$, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH;

A is a warhead;

X is selected from the group consisting of CH, $C(CH_3)$ and N; and

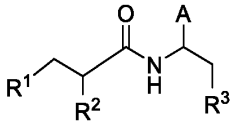
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

2. The compound is represented by:

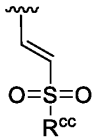
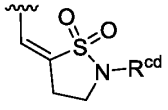


Formula II-A.

3. The compound is represented by:



Formula II-B.

4. A is selected from the group consisting of cyano, $–C(O)R^D$, $–C(O)CH_2N(R^bR^c)$, $–C(O)CH_2OC(O)R^D$, $–C(O)C(O)R^D$, $–(CH=CH)C(O)OR^D$, $–(CH=CCN)C(O)OR^D$, $–(CH=CCN)C(O)(NH)R^D$, $–CH(CN)(OH)$, $-CH(CN)(NR^bR^c)$,  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} – $N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

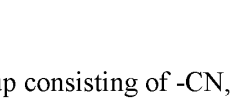
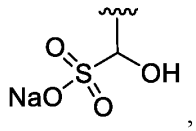
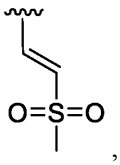
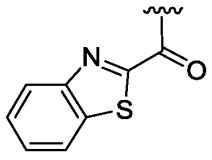
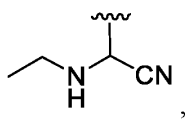
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

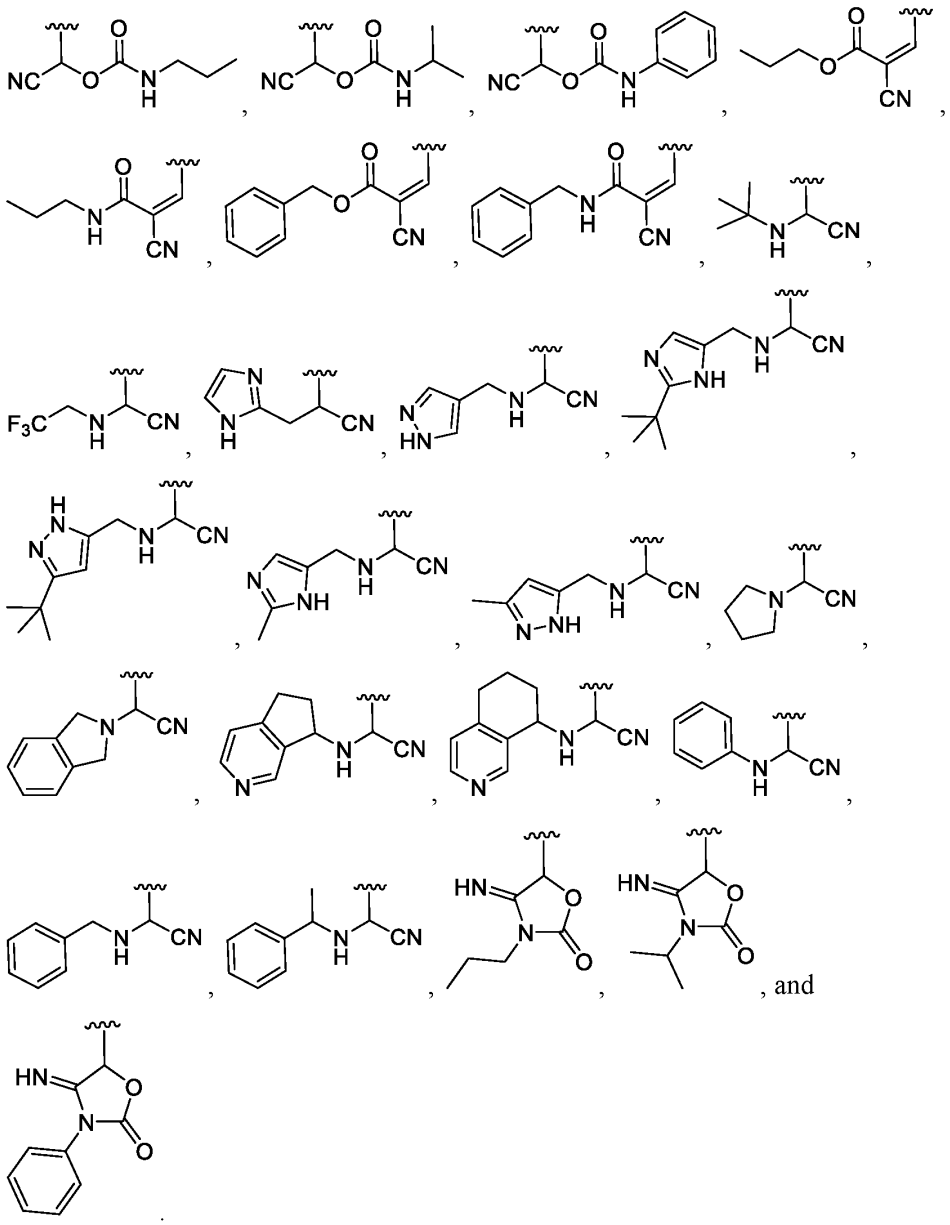
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

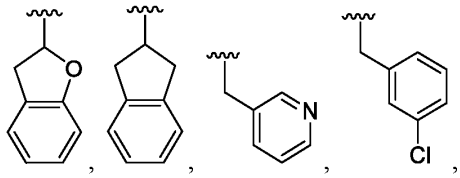
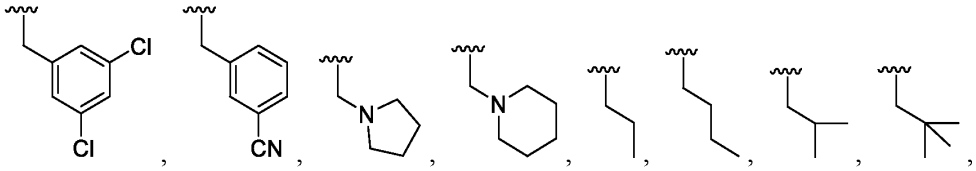
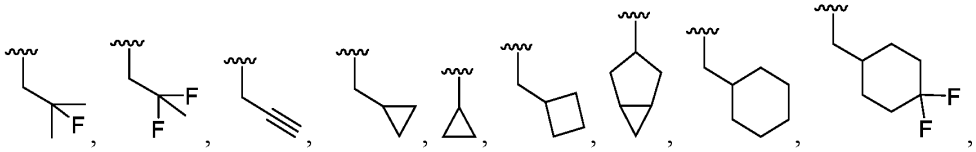
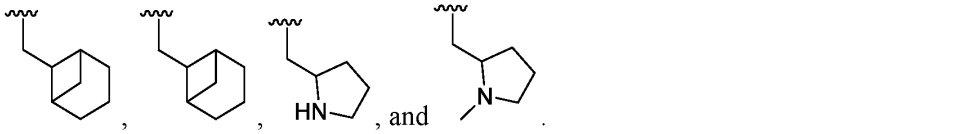
R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -$N(R^bR^c)$, wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

R^b and R^c are each selected from the group consisting of hydrogen, – $CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

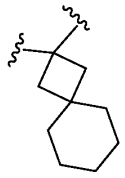
5. A is selected from the group consisting of -CN,  , ,  ,  ,  ,  ,



6. R^{1a} is selected from the group consisting of  ,  ,  ,  , and .

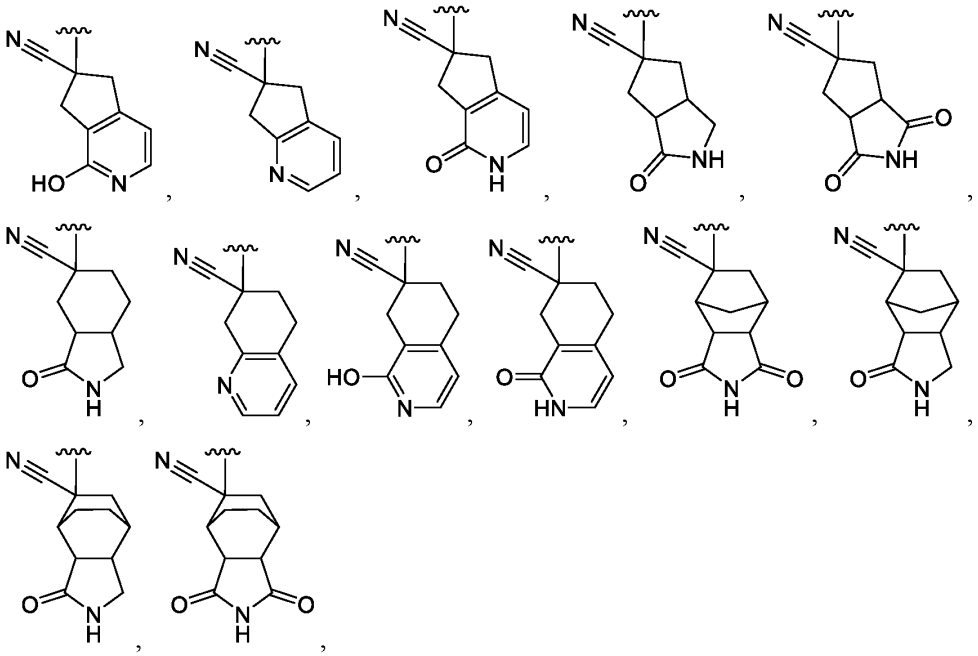
7. R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

8. R^{1b} is hydrogen.

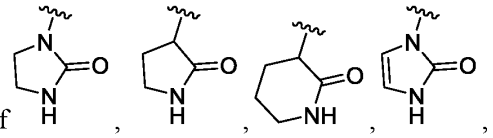
9. R^{1a} and R^{1b} are joined to together to form  .

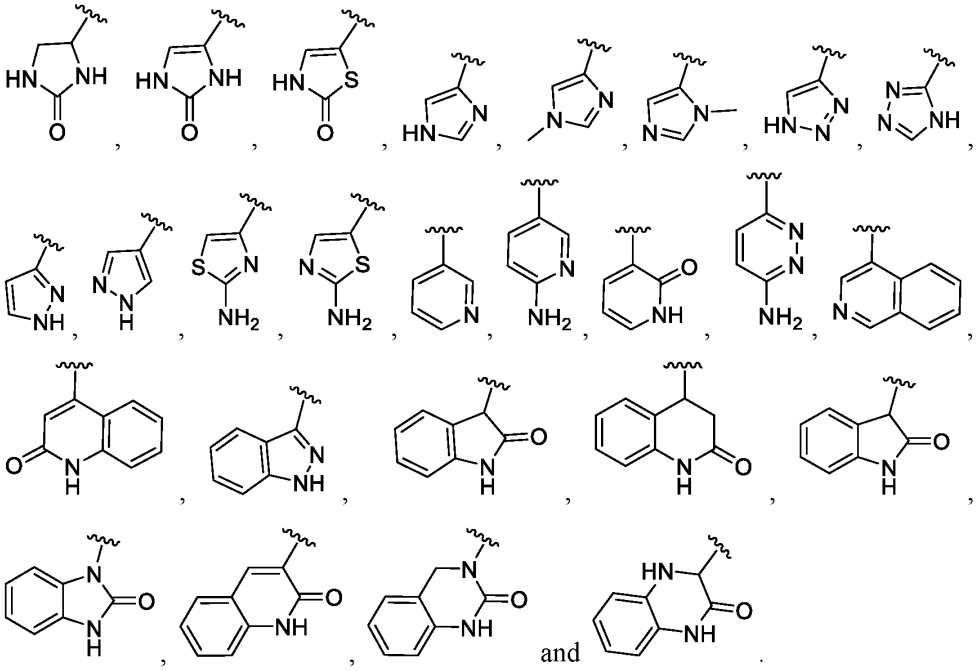
10. R^{3a} is a 4-10 membered heterocycle substituted by A.

11. R^{3a} is selected from the group consisting of

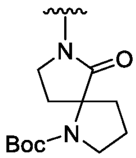
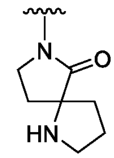
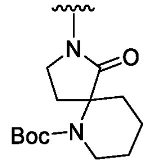


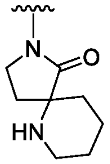
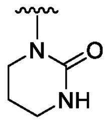
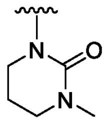
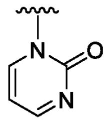
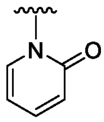
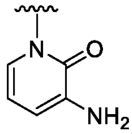
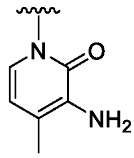
12. R^3 is a 4-10 membered heterocycle.

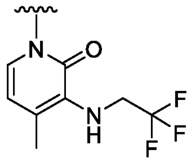
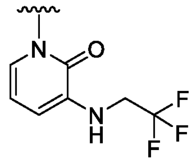
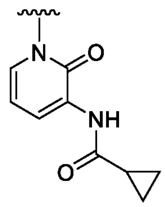
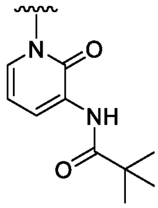
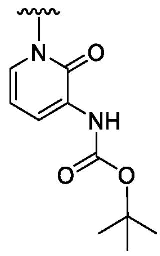
13. R^3 is selected from the group consisting of 

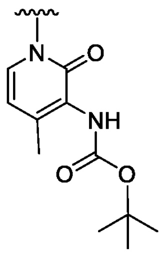
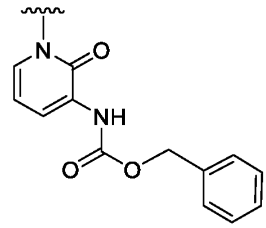
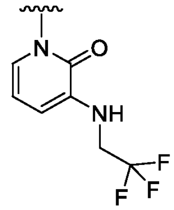
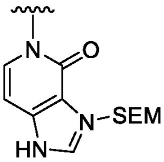


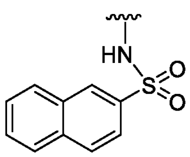
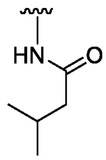
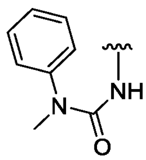
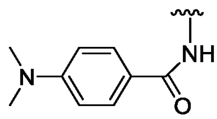
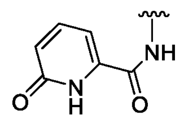
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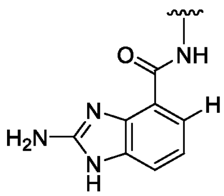
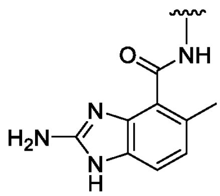
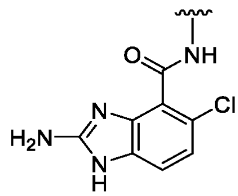
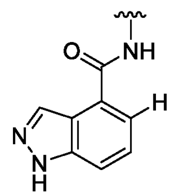
14. R^2 is selected from the group consisting of  ,  ,  ,

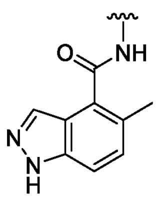
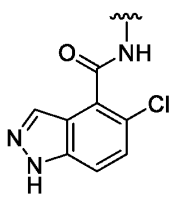
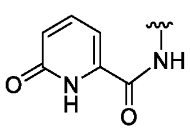
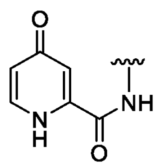
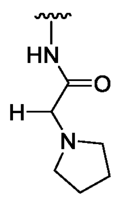
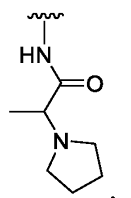
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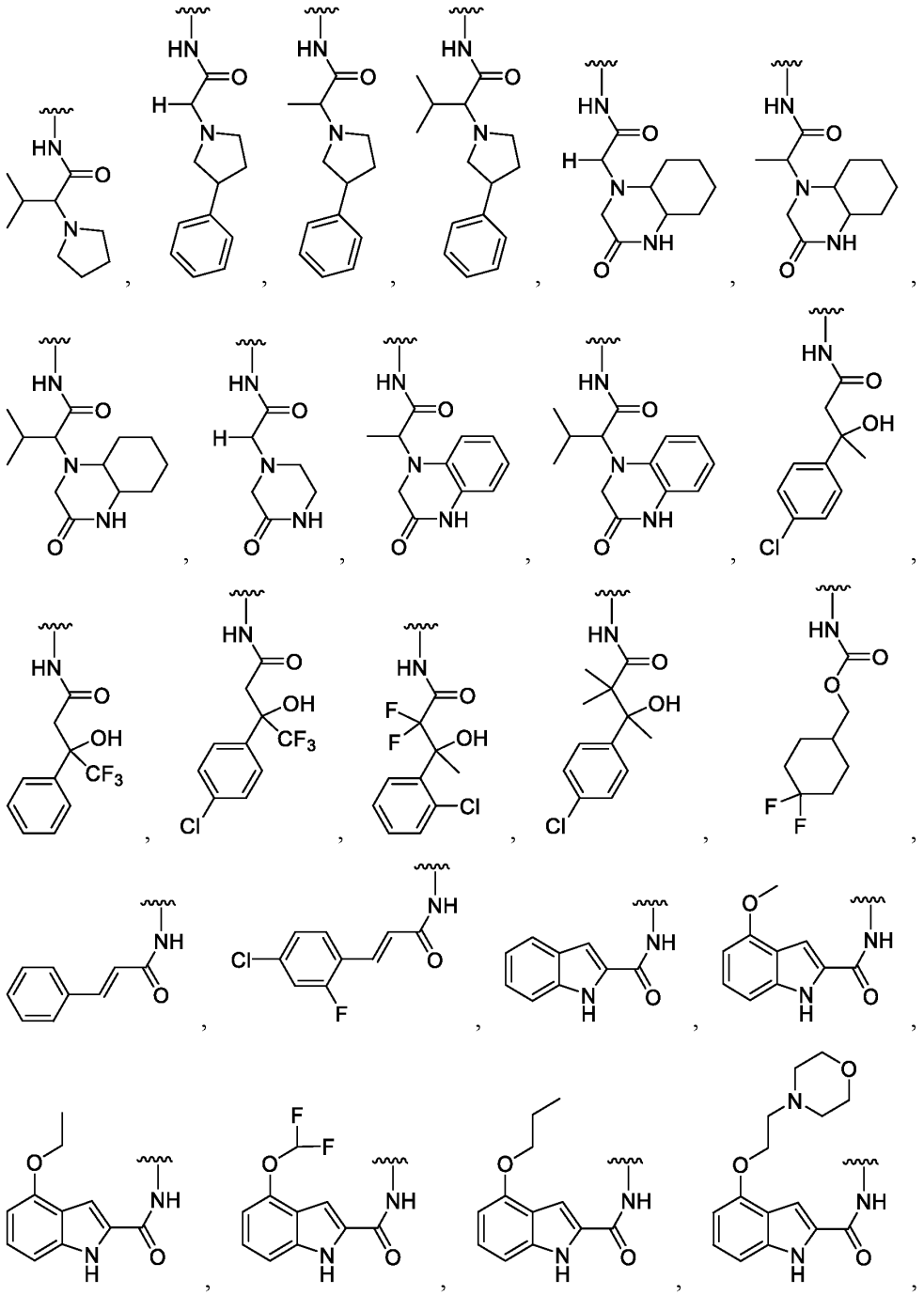
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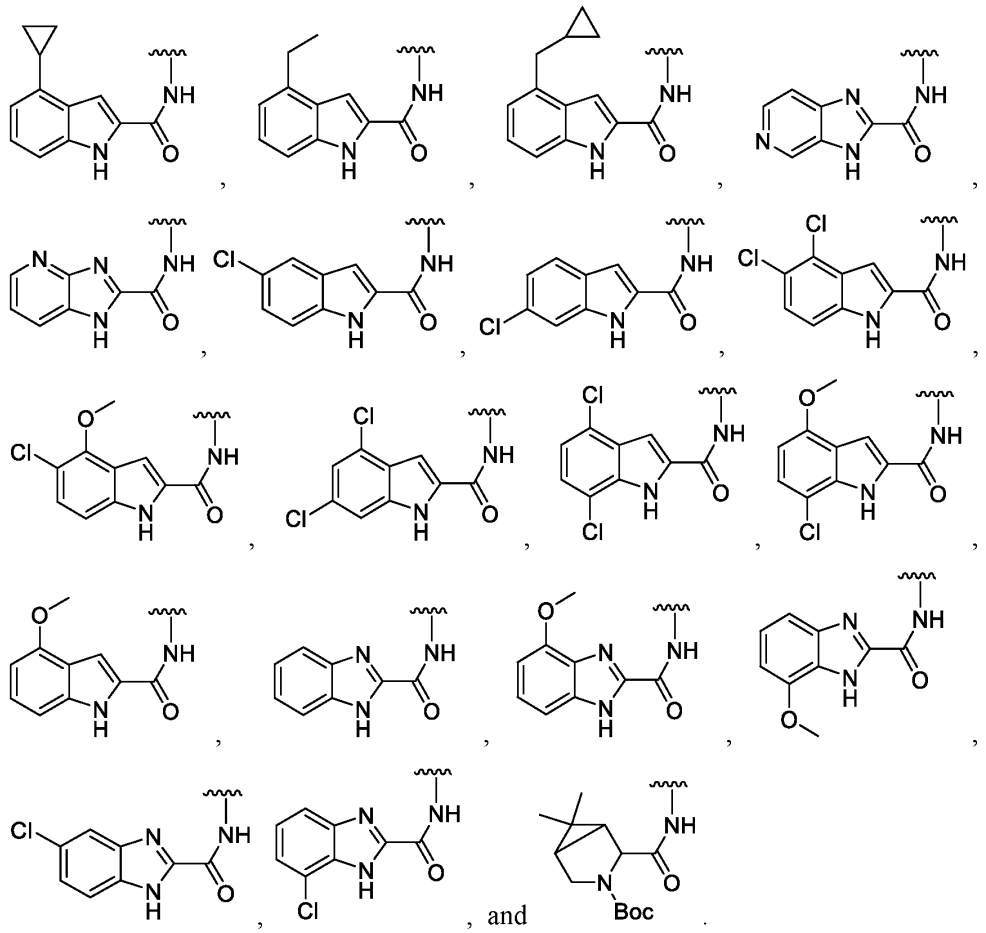
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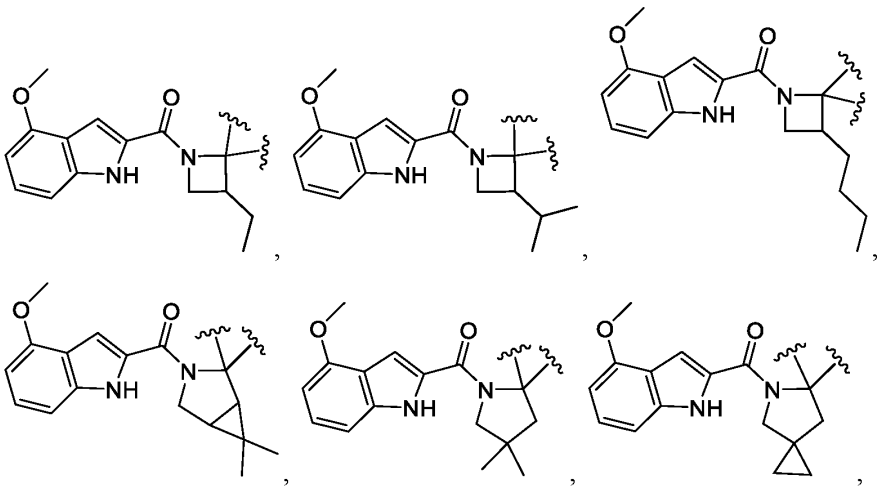
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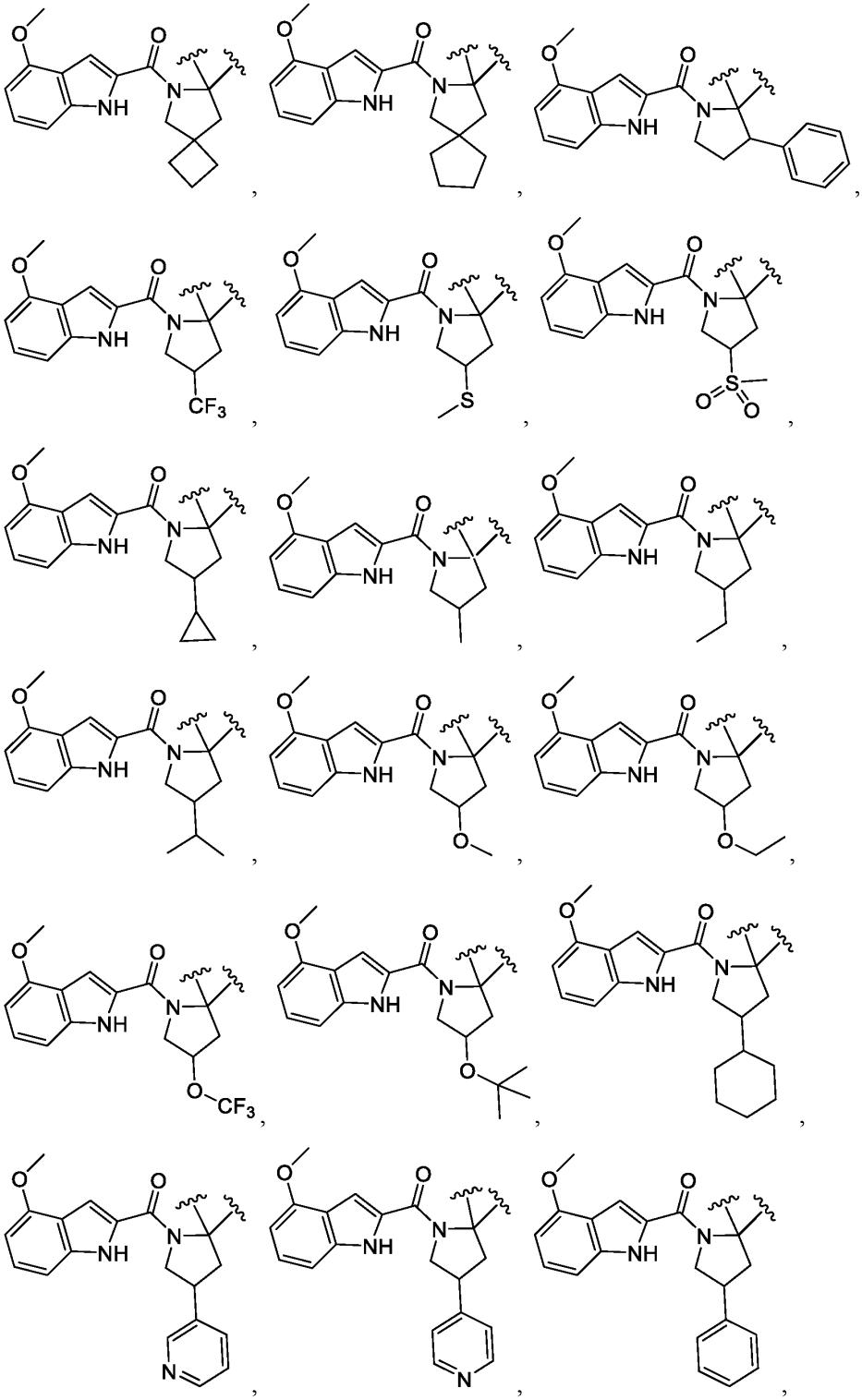
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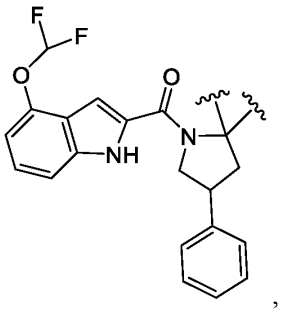
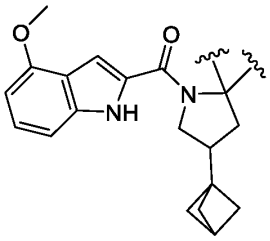
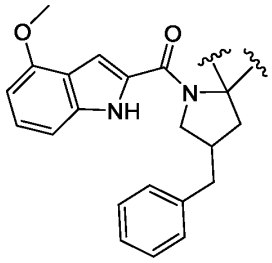
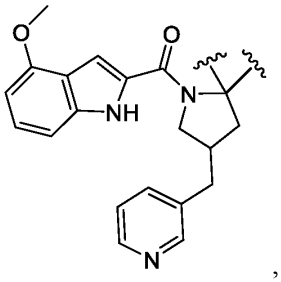
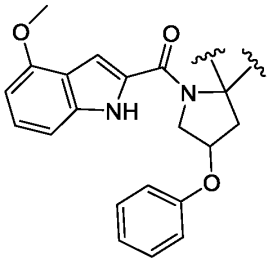
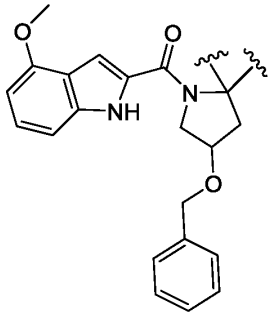
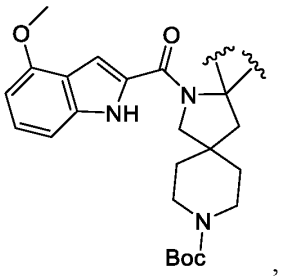
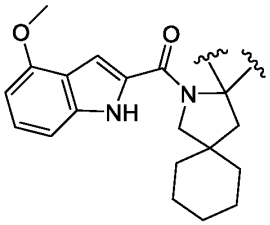
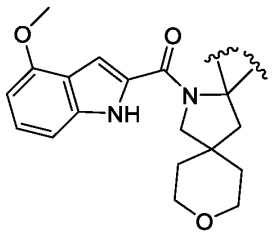
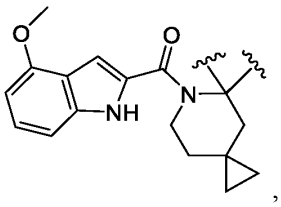
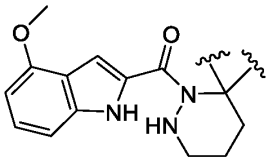
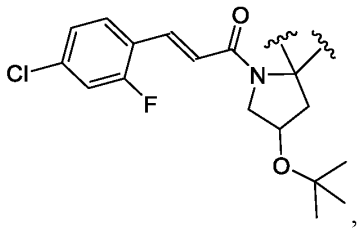
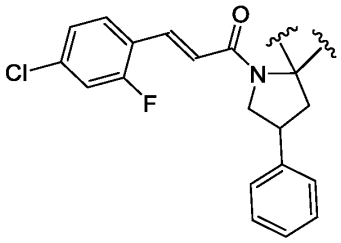
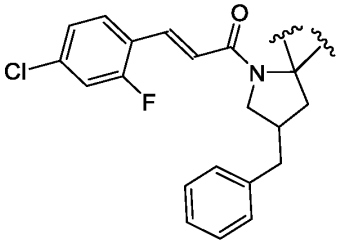
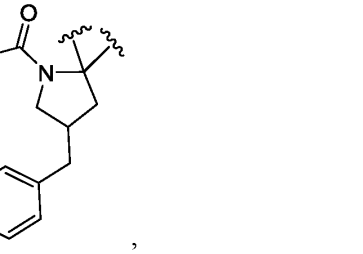




15. R^{1a} and R^2 are joined to together to form the heterocycle selected from the group consisting of:



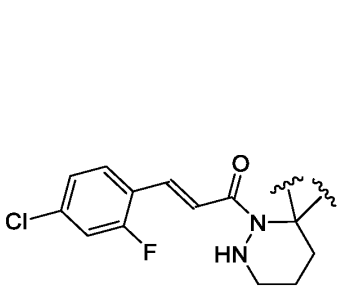
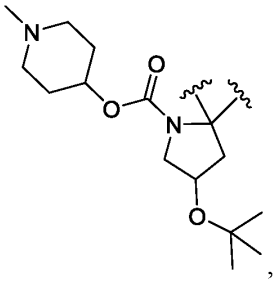
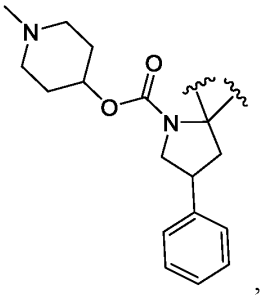
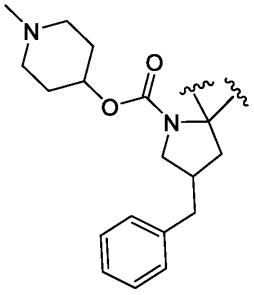
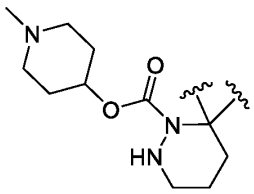
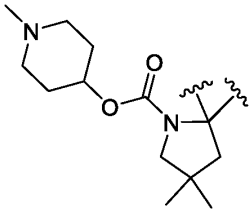
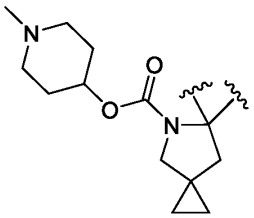
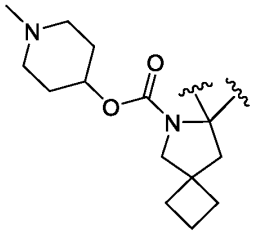
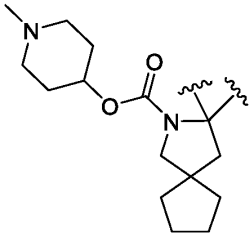
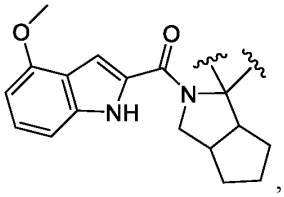
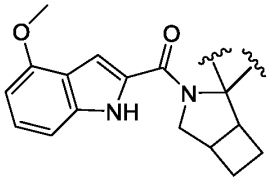
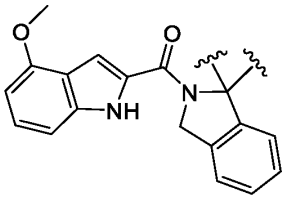
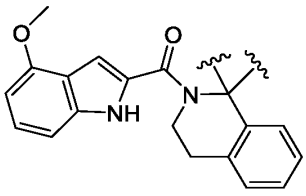
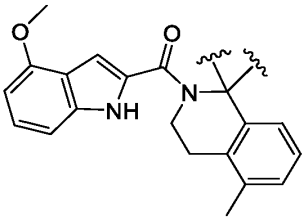
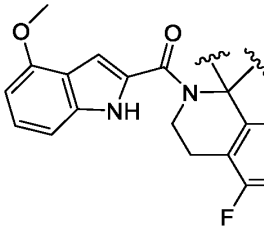



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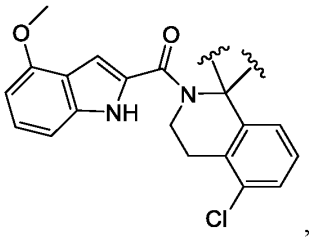
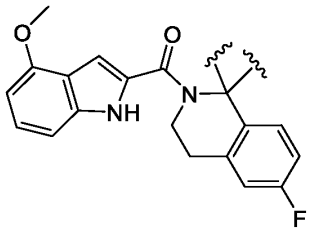
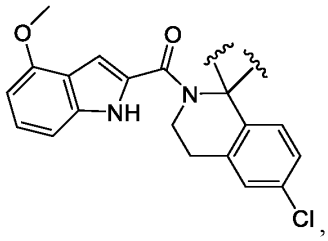
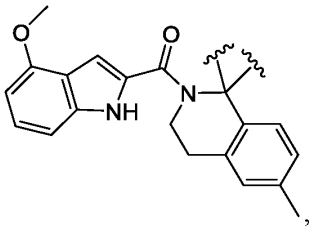
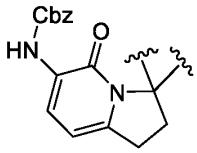
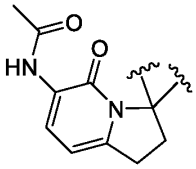
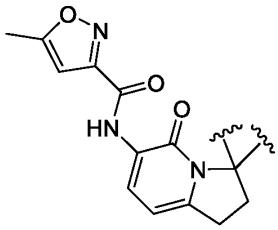
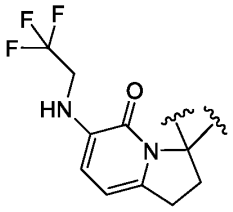
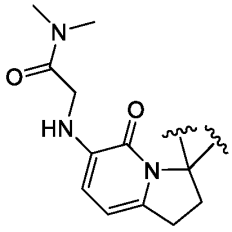
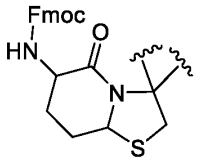
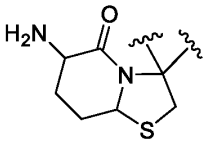
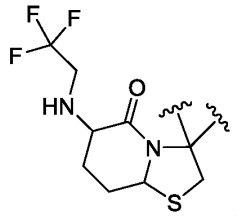
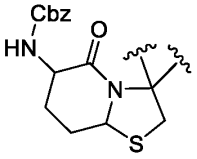
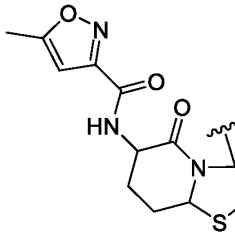
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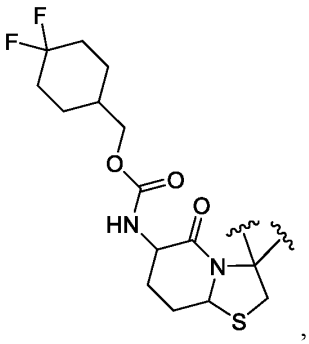
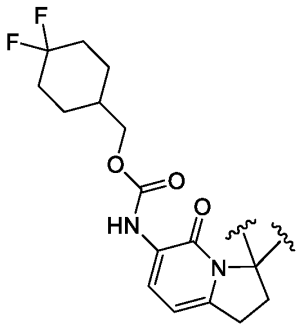
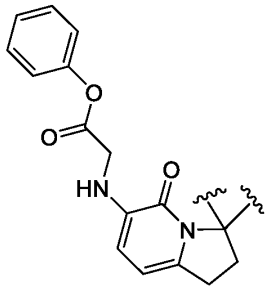
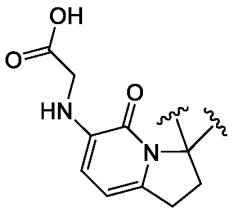
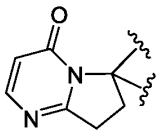
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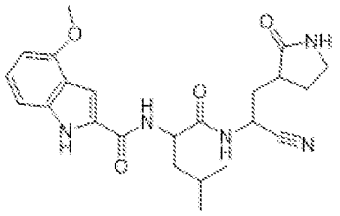
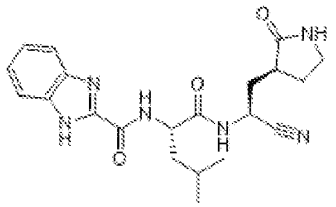
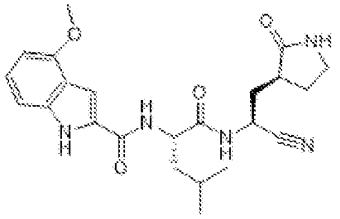
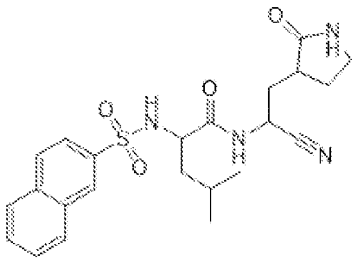
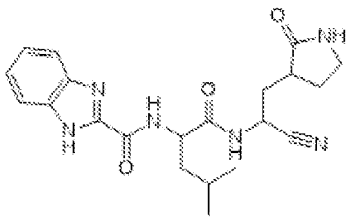
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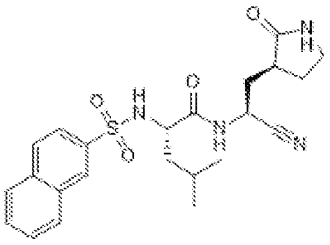
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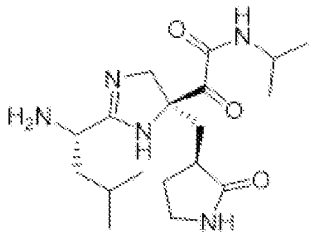
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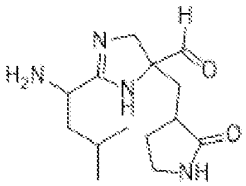

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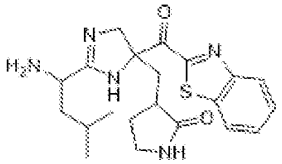
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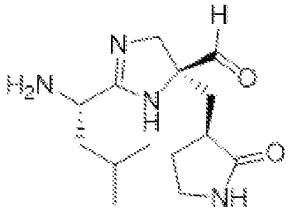

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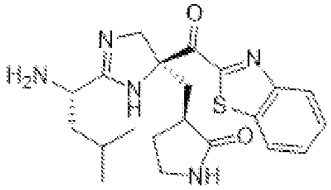

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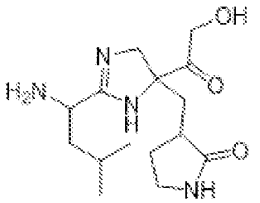

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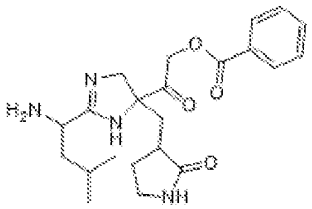

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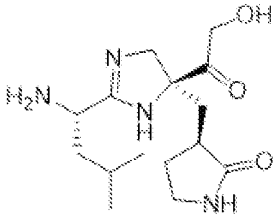

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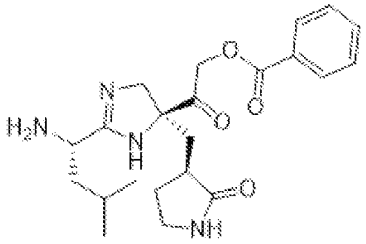

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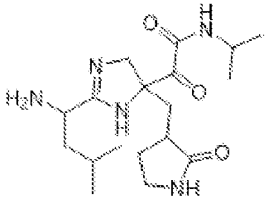

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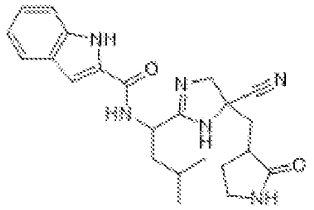

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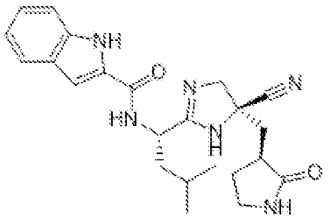

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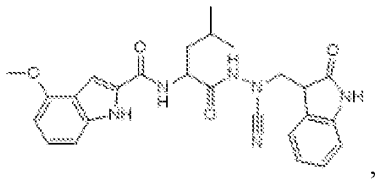

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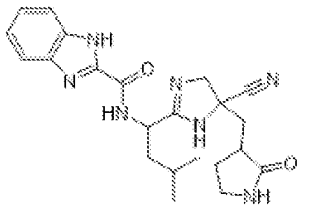

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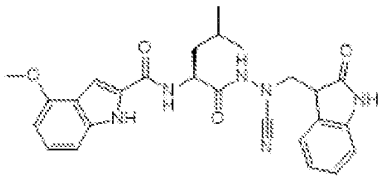
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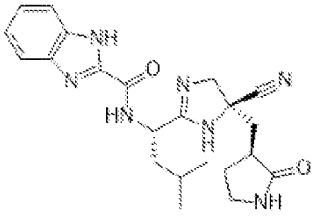
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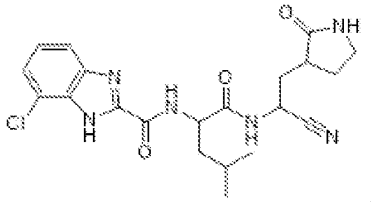
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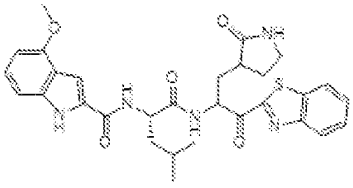
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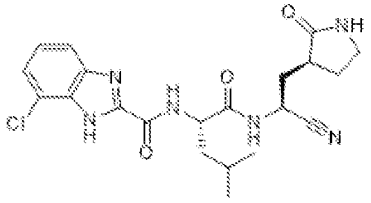
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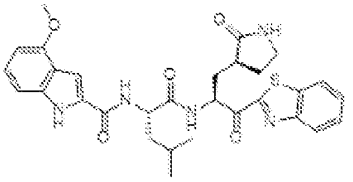
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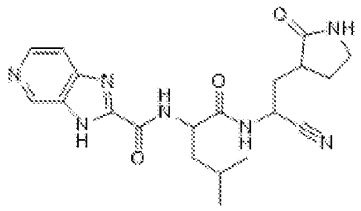
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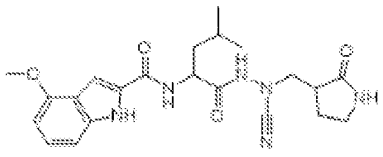
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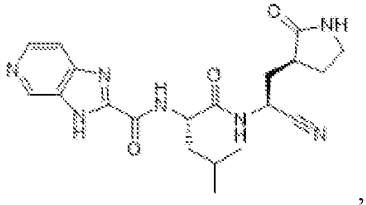
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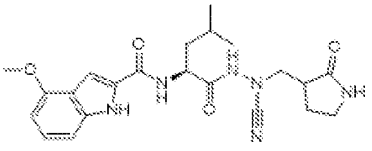
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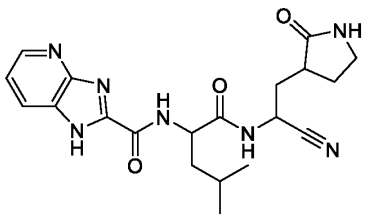
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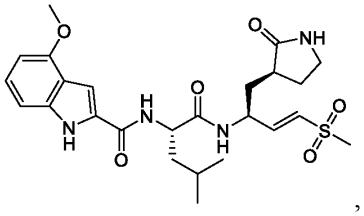
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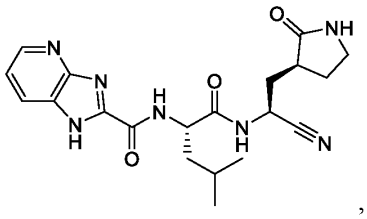
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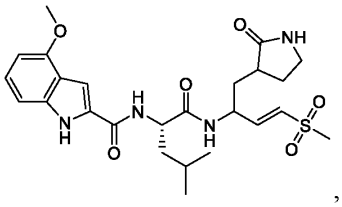
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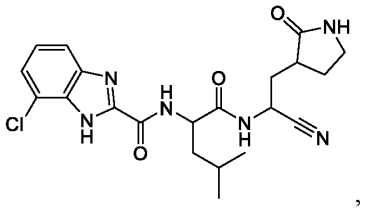
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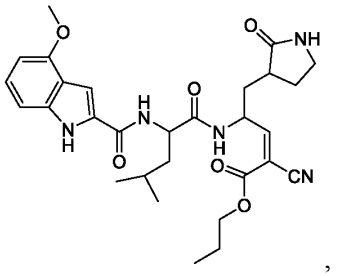
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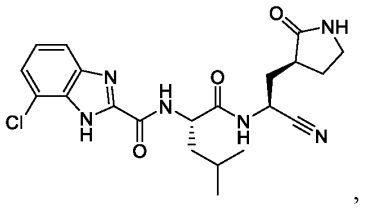
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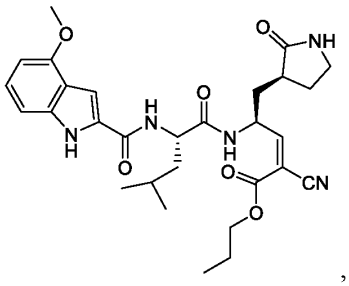
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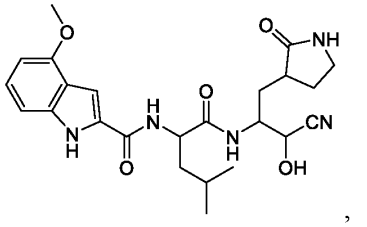
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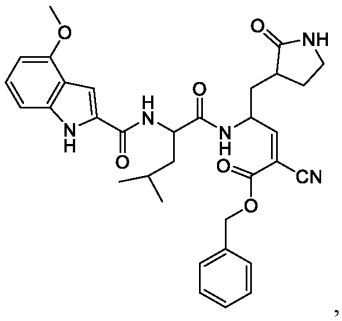
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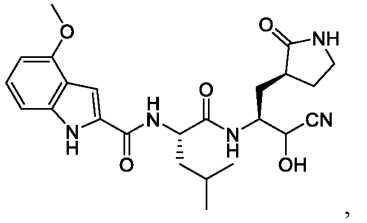
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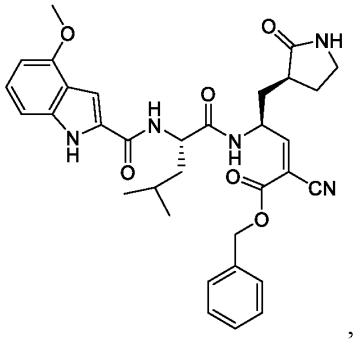
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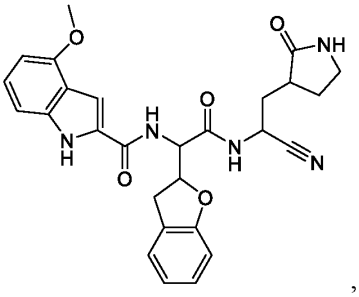
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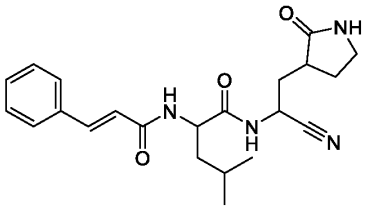
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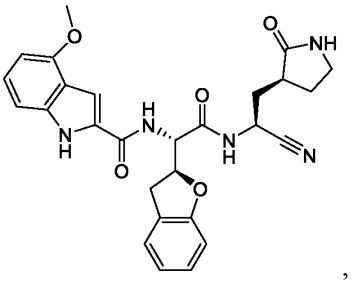
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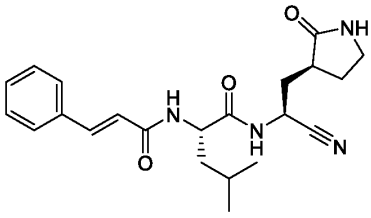
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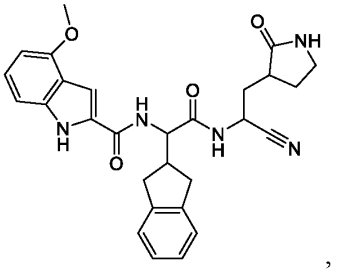
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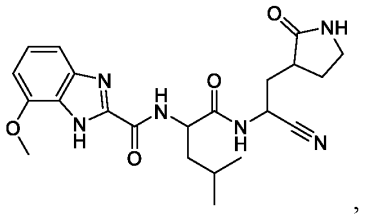
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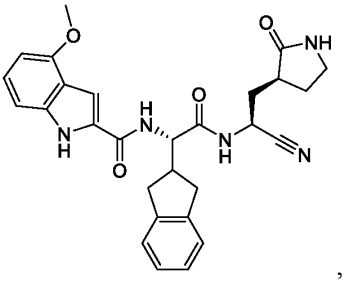
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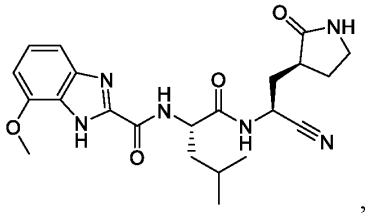
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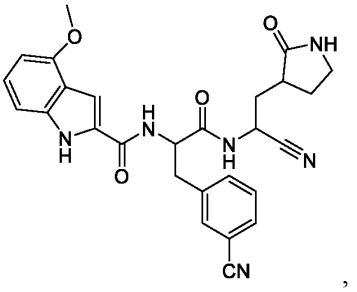
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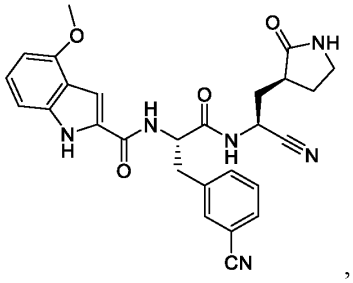
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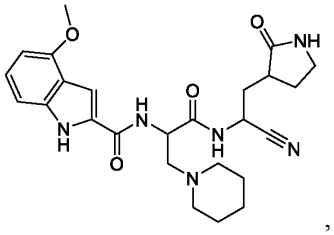
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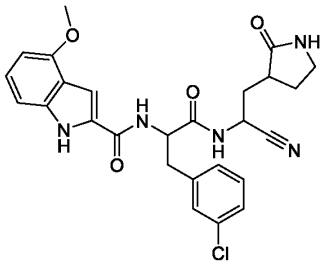
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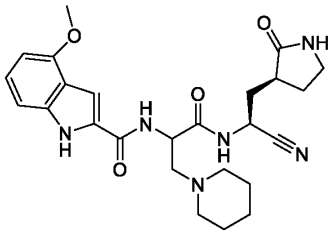
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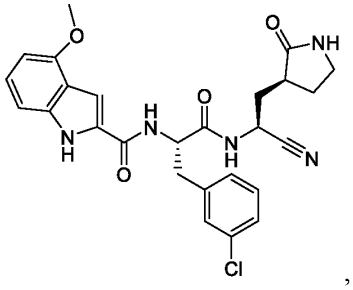
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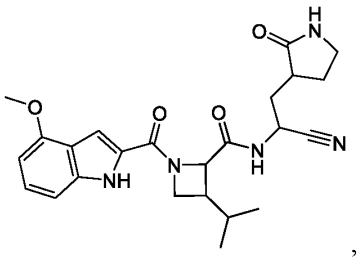
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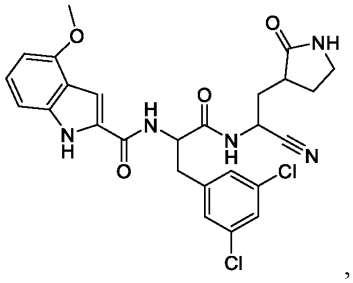
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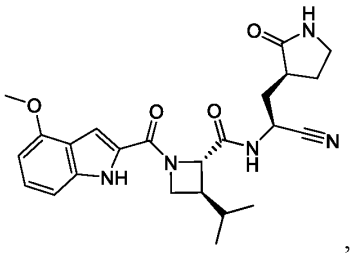
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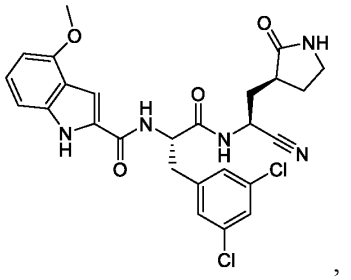
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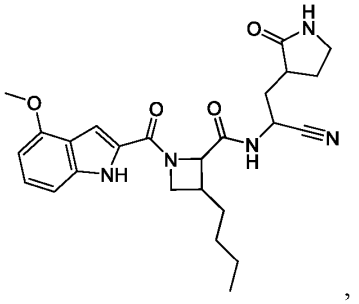
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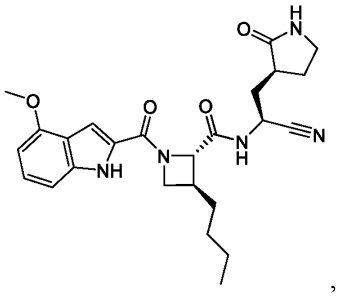
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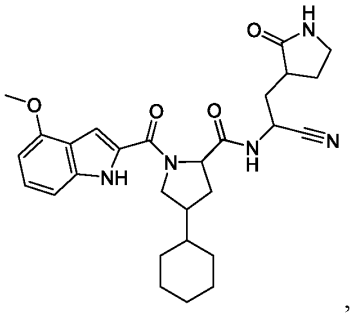
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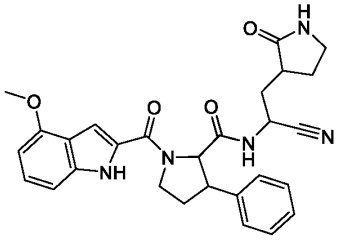
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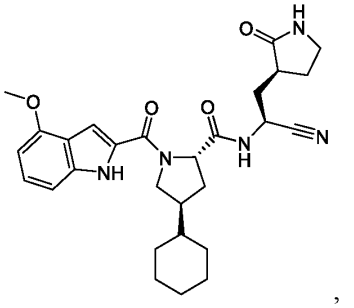
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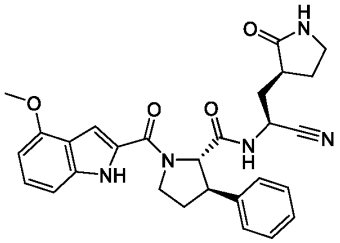
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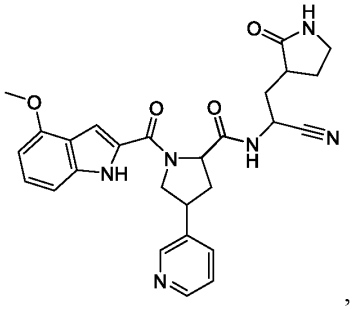
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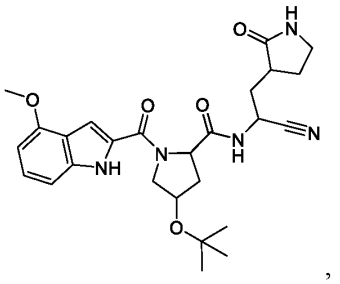
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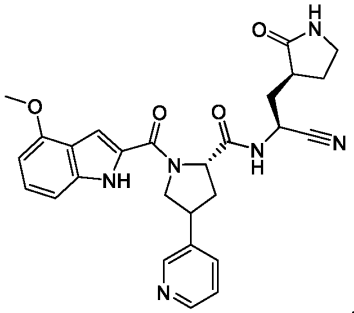
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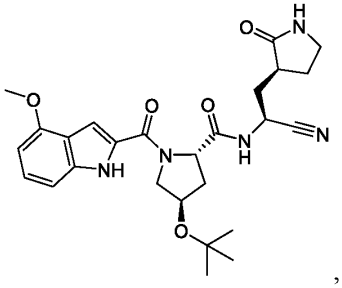
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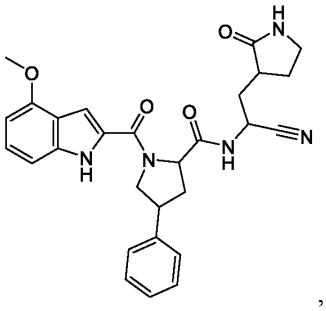
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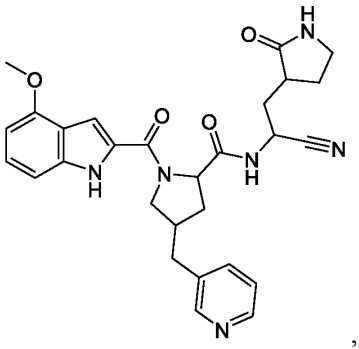
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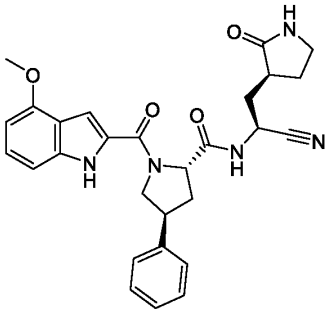
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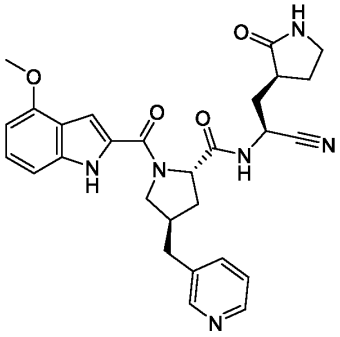
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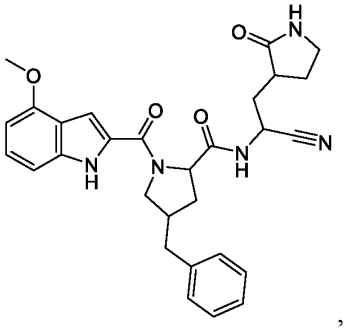
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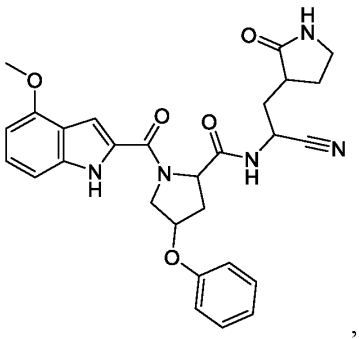
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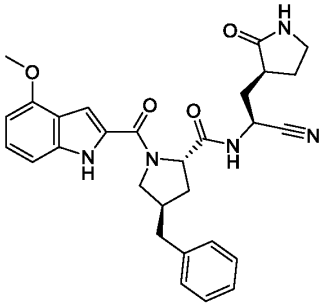
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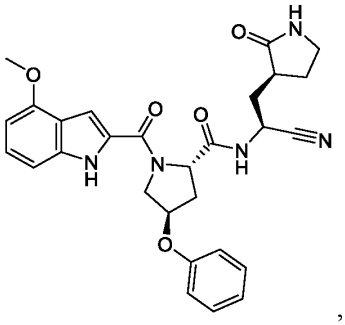
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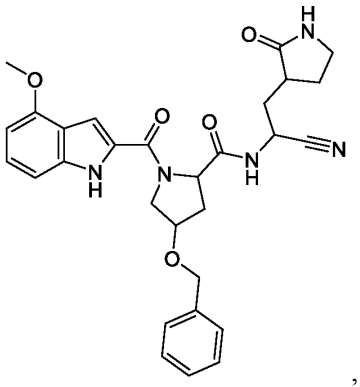
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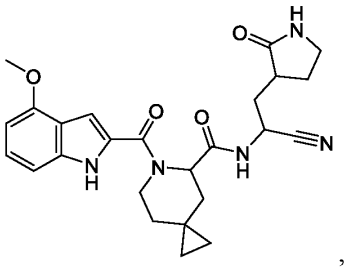
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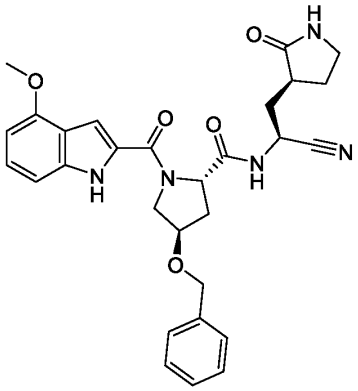
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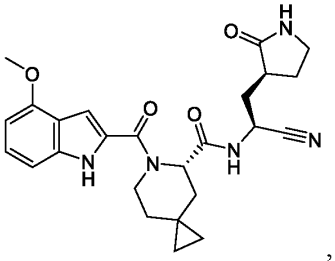
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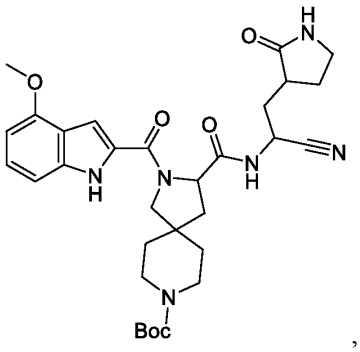
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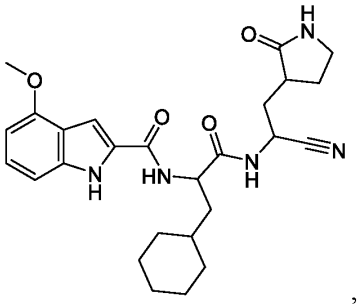
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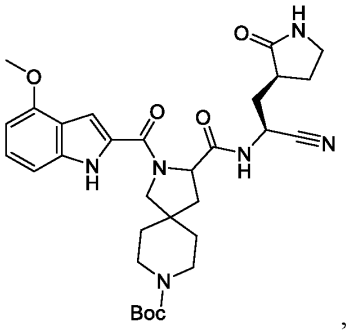
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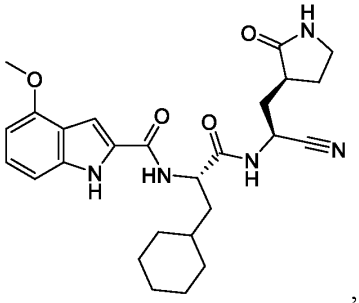
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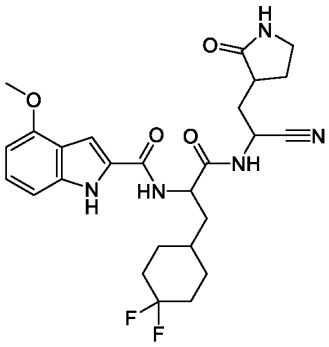


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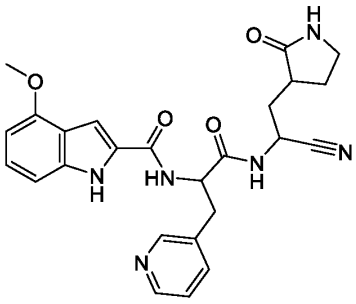


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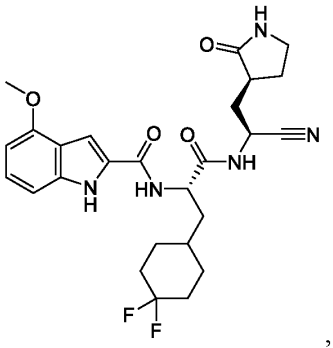
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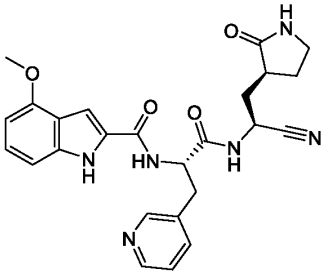
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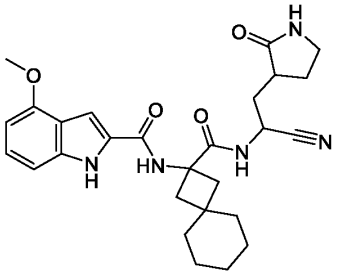
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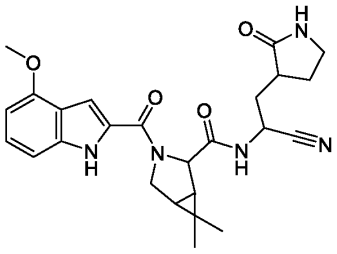
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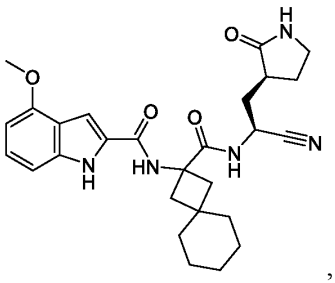
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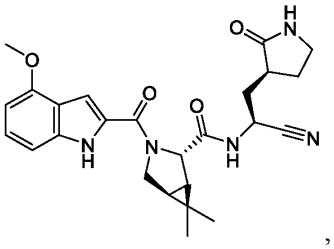
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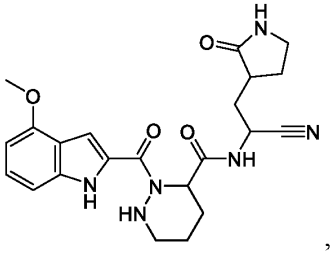
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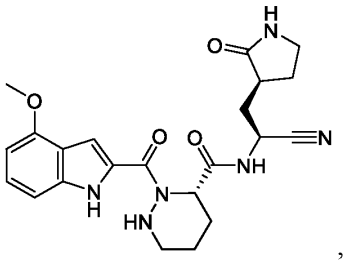
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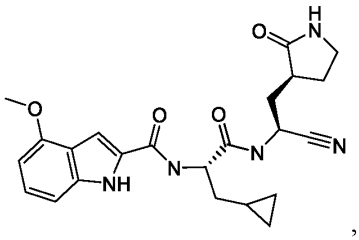


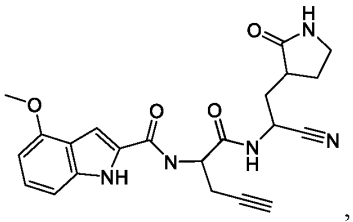
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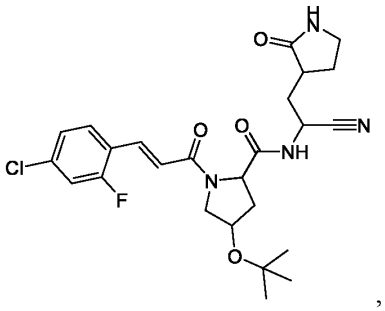


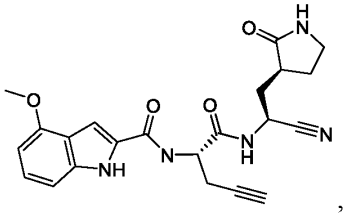
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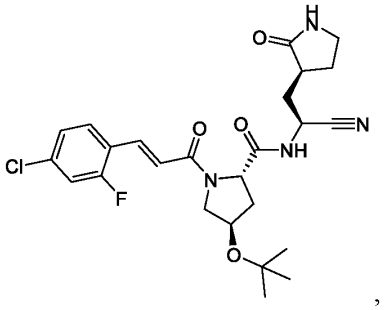

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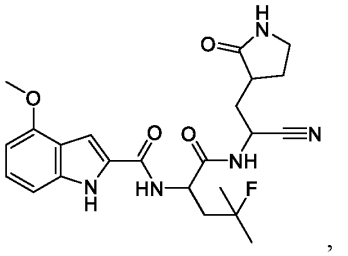

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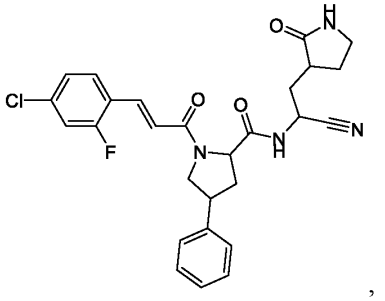

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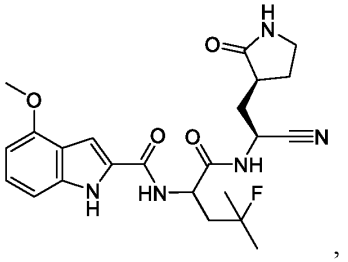

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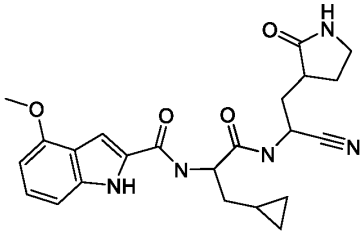

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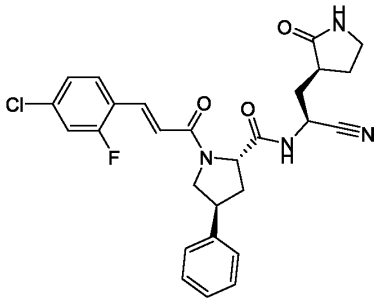

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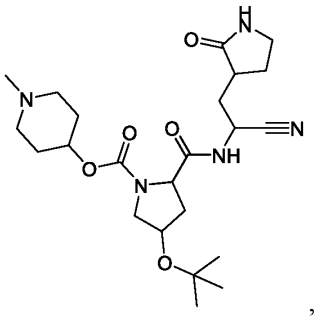

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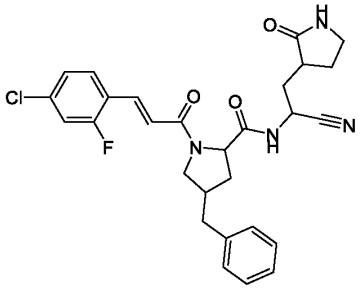

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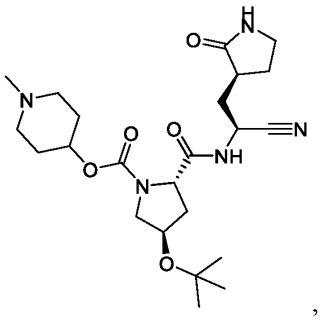
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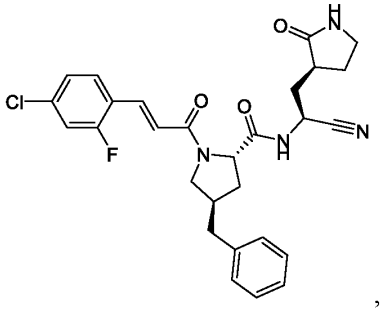
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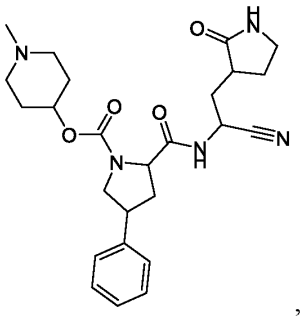
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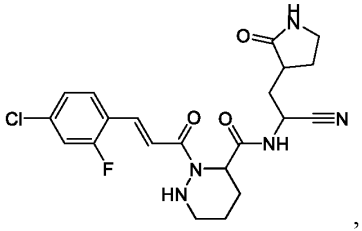
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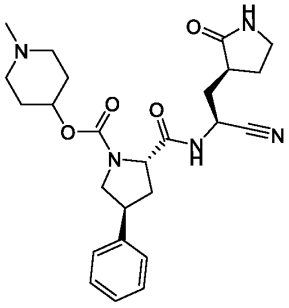
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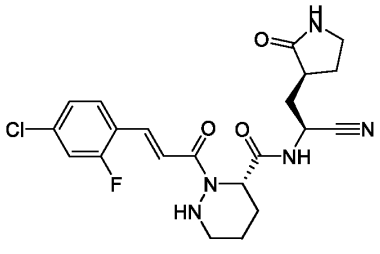
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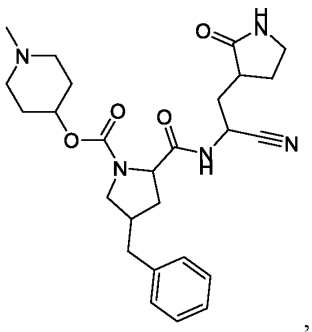
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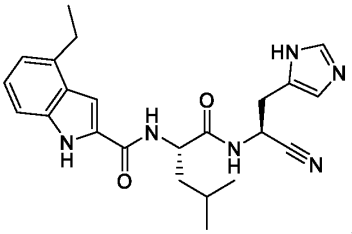
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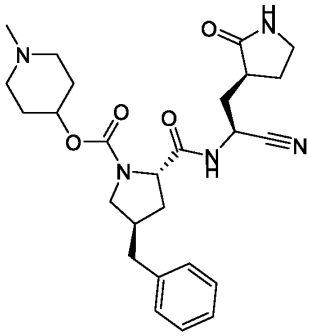
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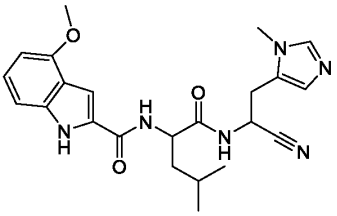
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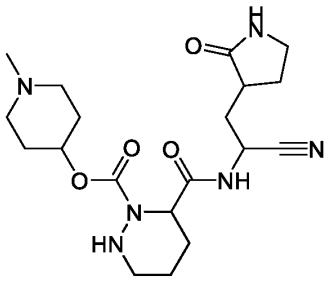
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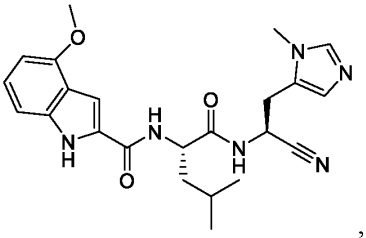
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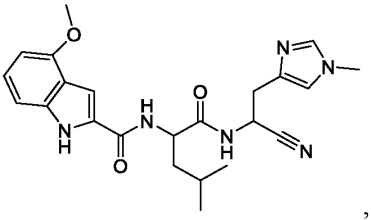
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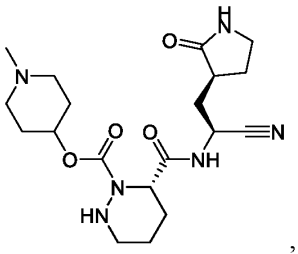
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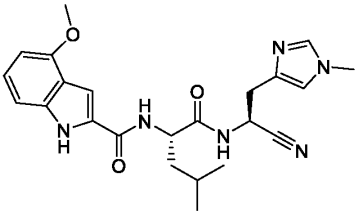
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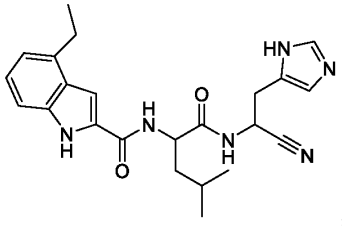
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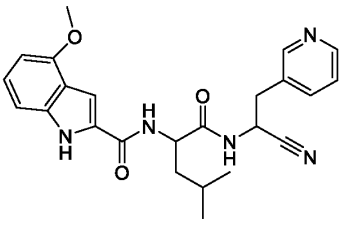
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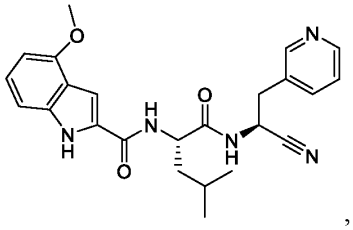
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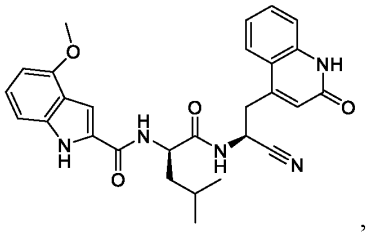
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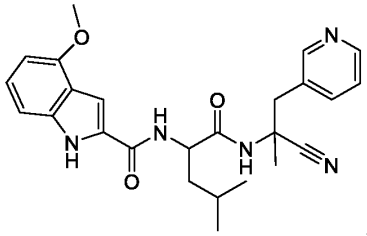
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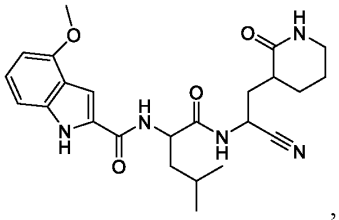
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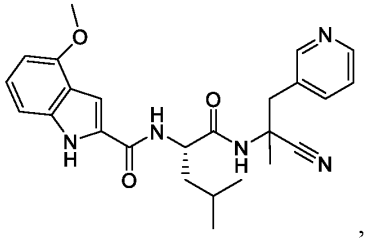
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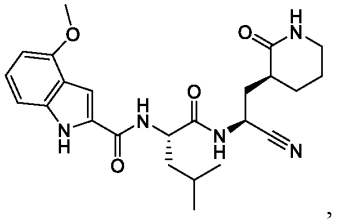
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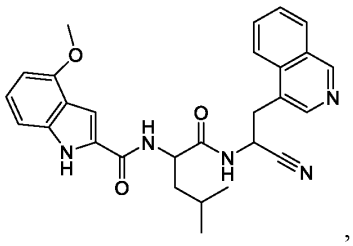
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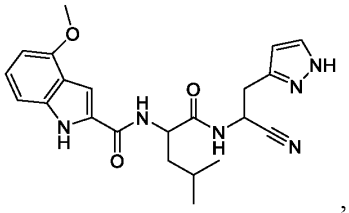
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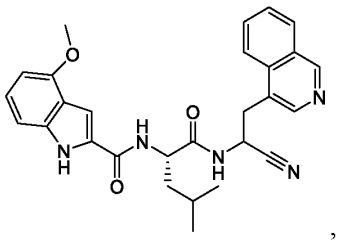
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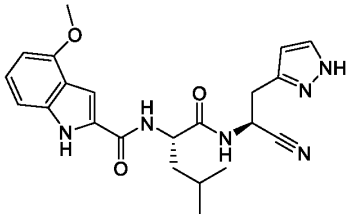
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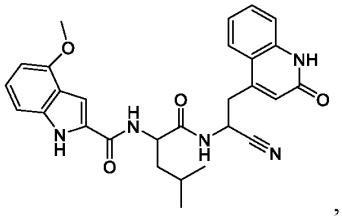
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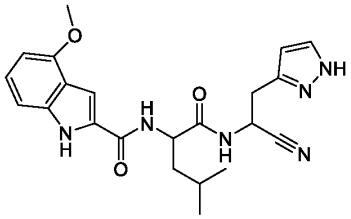
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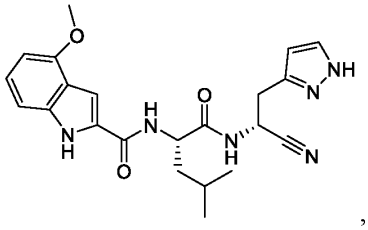
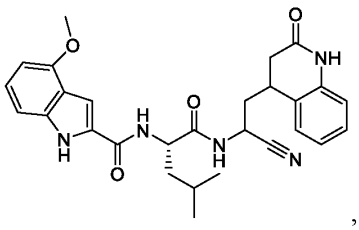
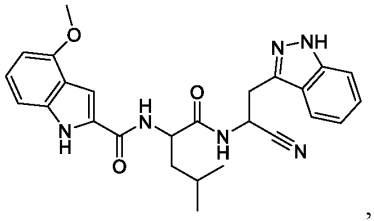
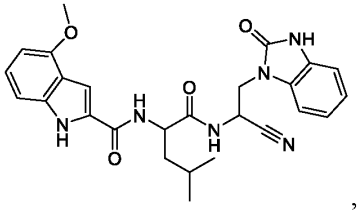
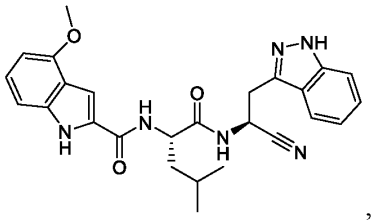
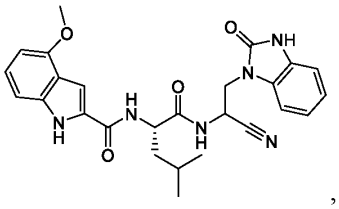
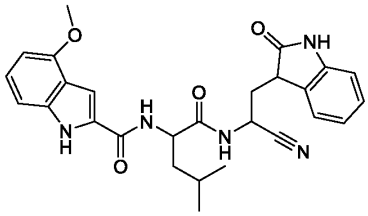
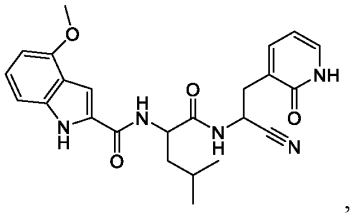
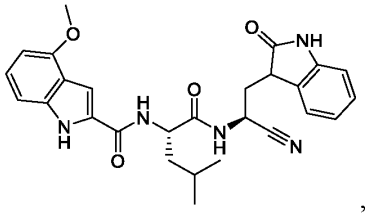
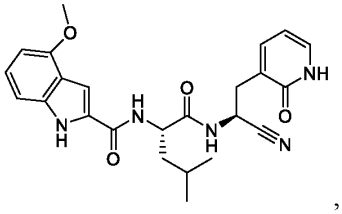
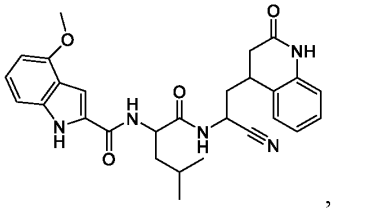
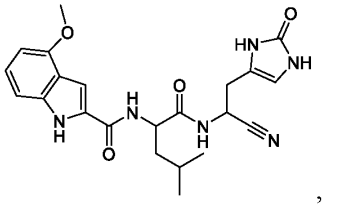
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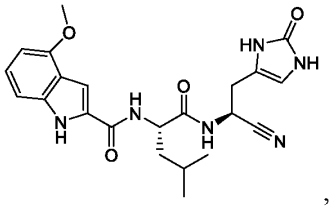
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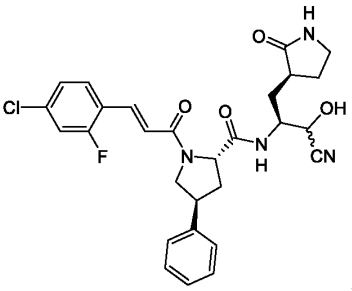
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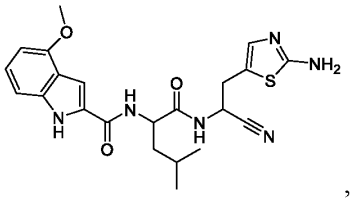
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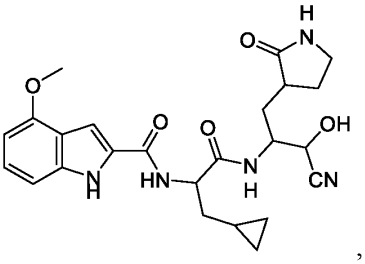
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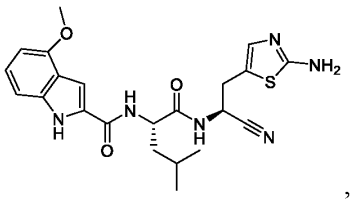
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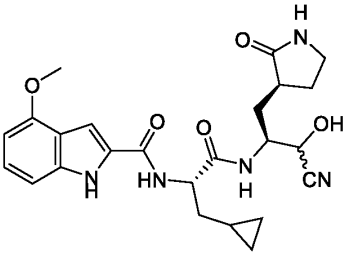
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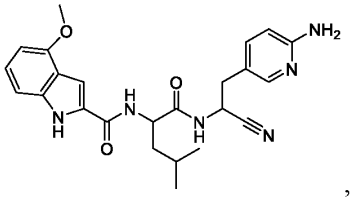
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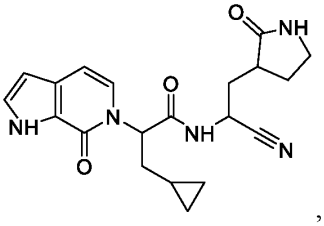
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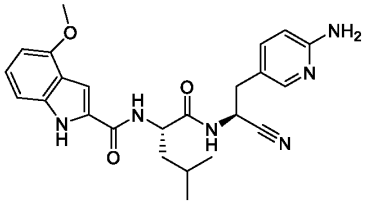
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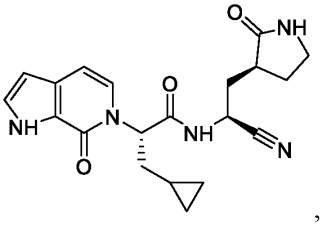
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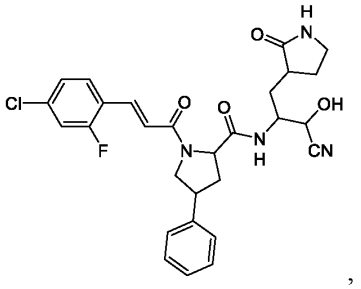
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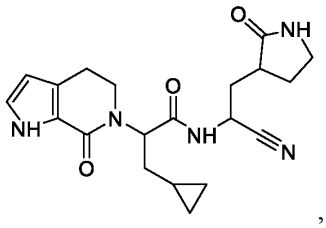


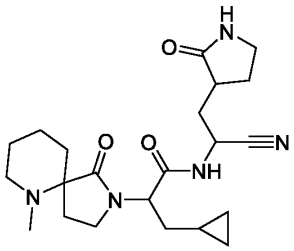
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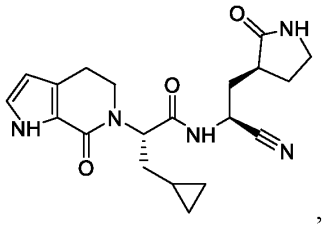


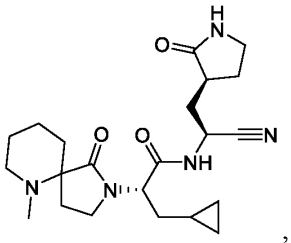
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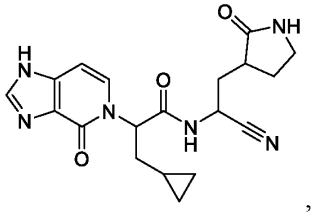
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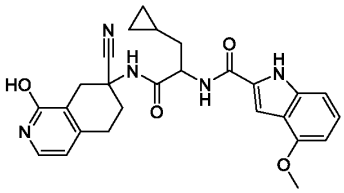

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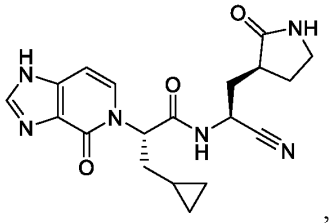

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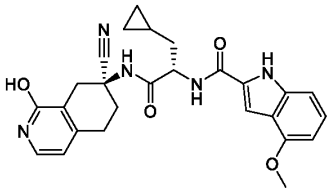

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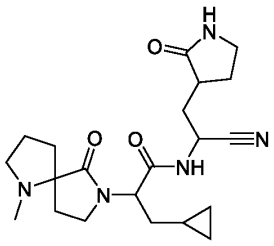

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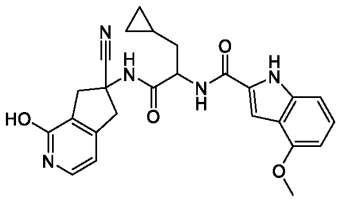

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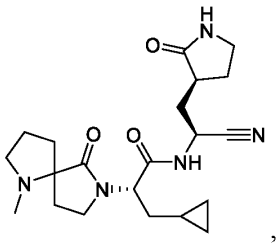

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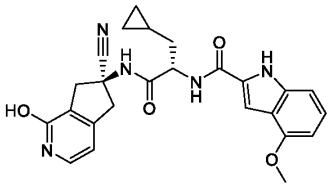

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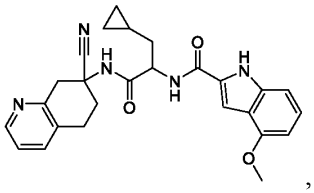

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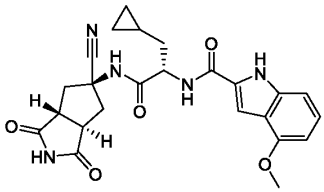

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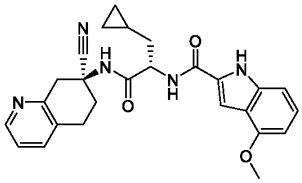

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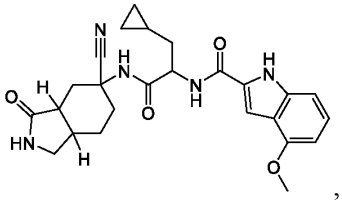

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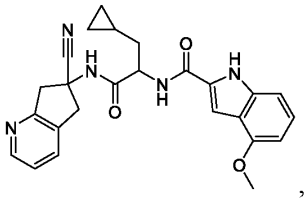

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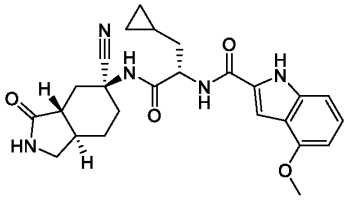

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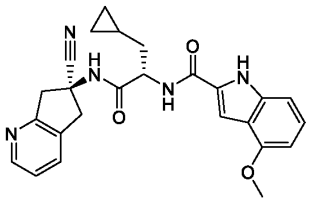

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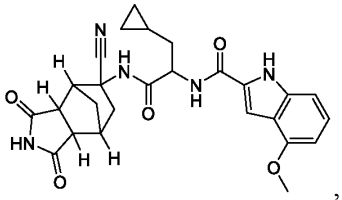

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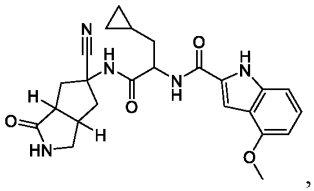

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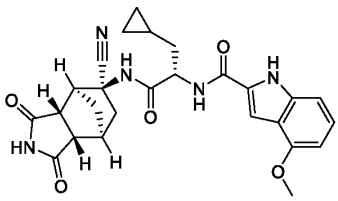

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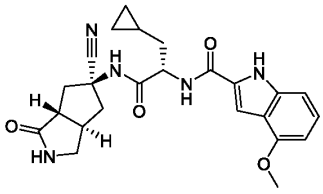

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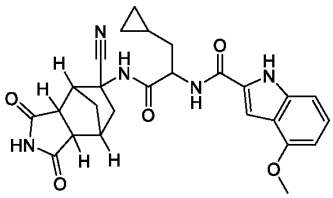

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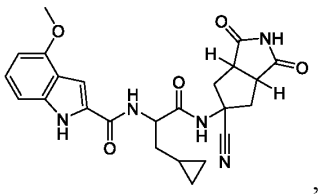

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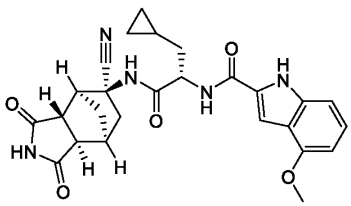

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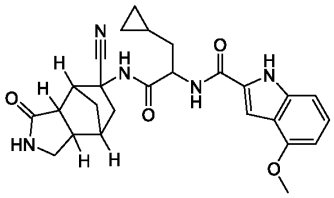

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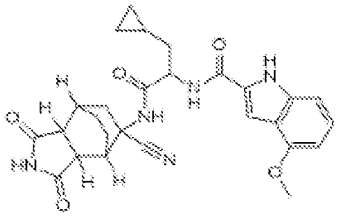

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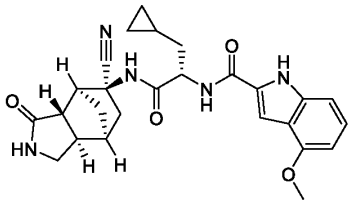

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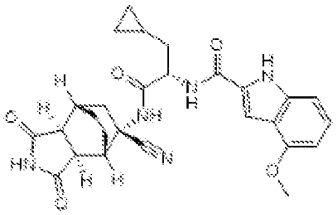

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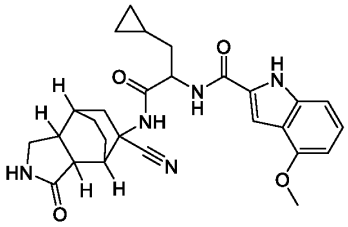

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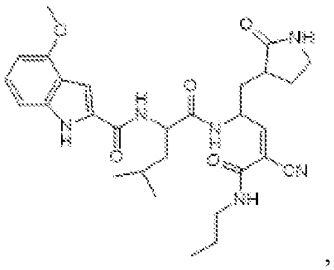

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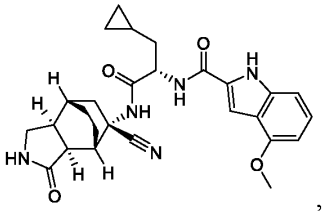

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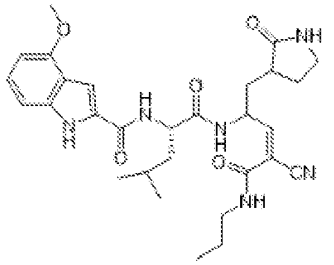

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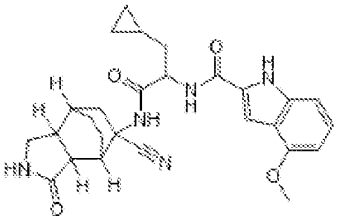

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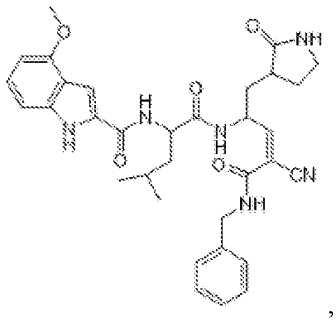

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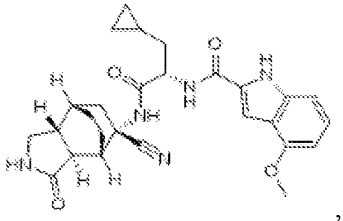

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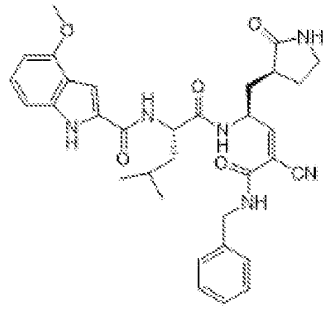

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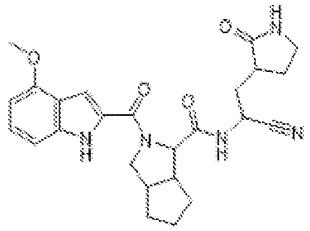

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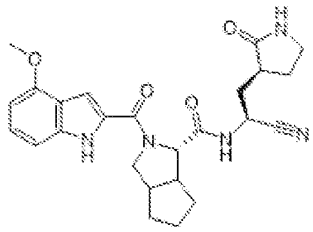
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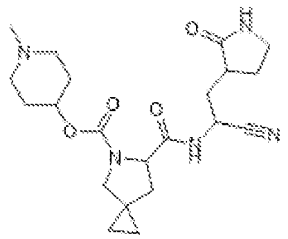
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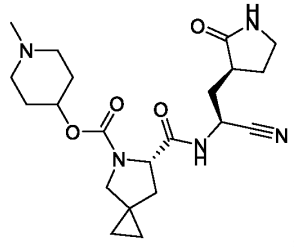
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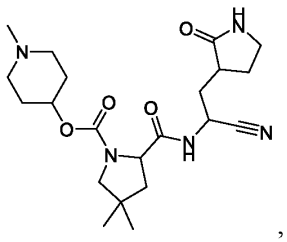
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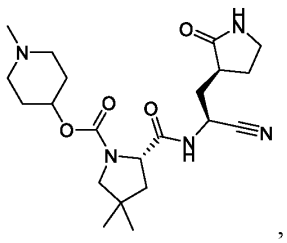
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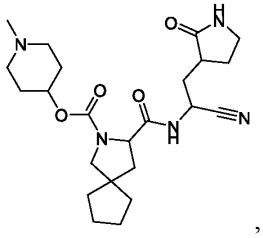
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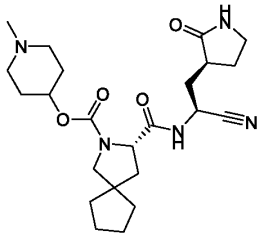
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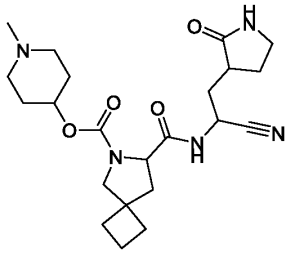
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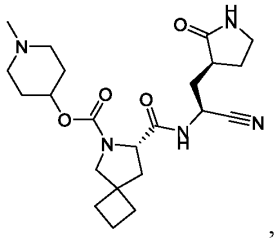
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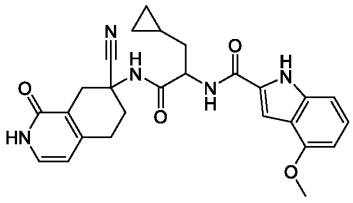
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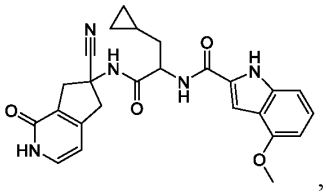


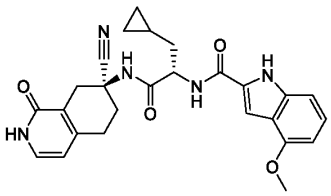
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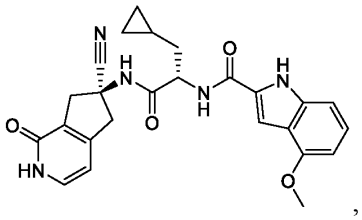


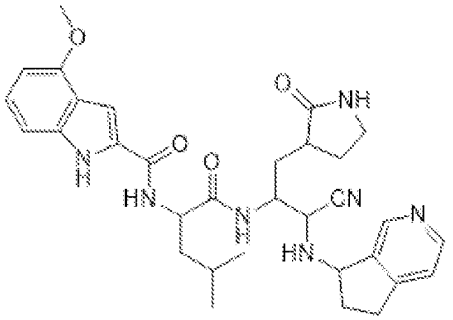
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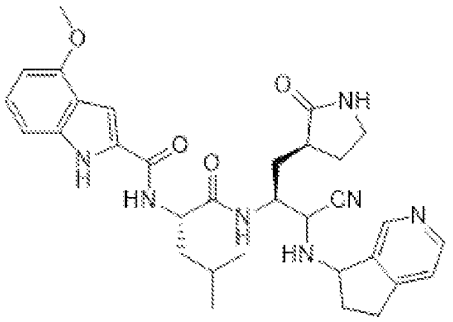

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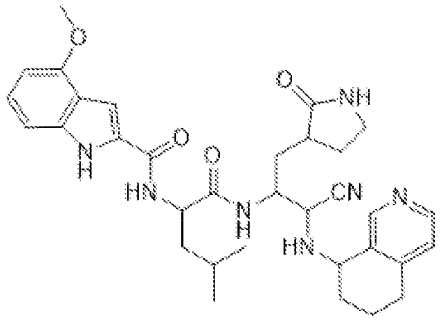

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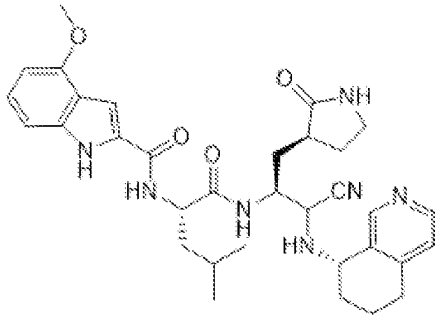

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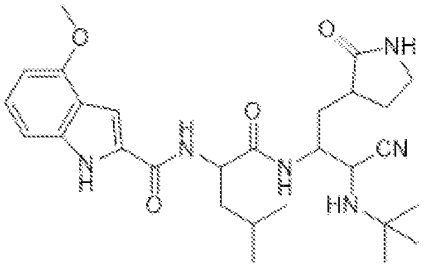

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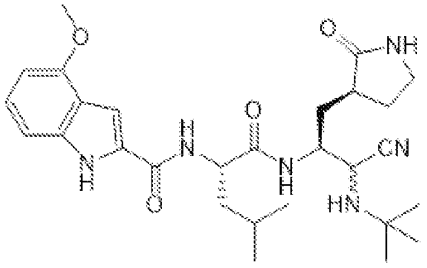

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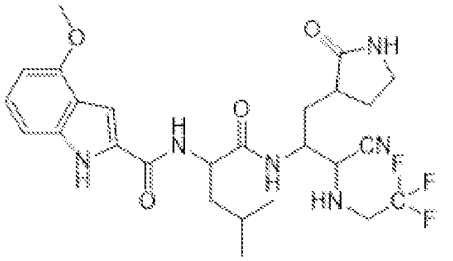

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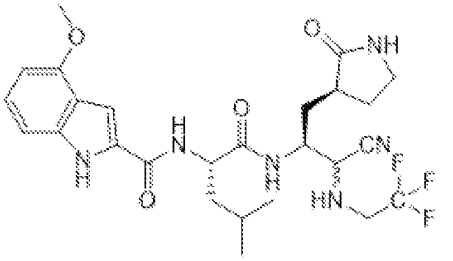

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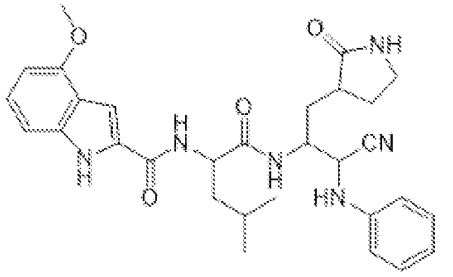

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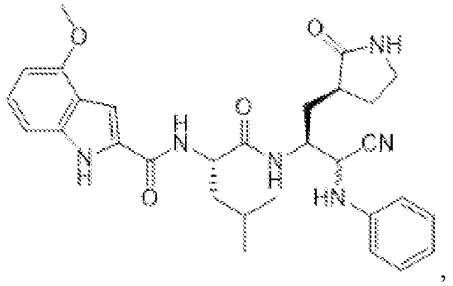

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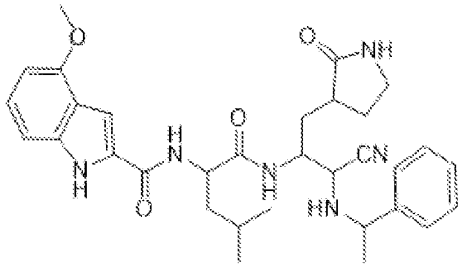

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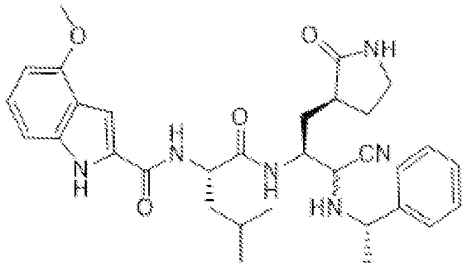

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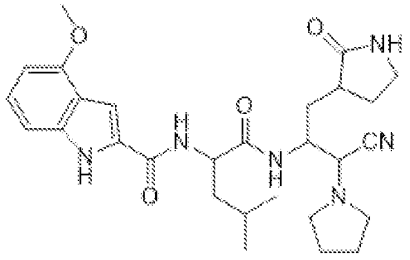

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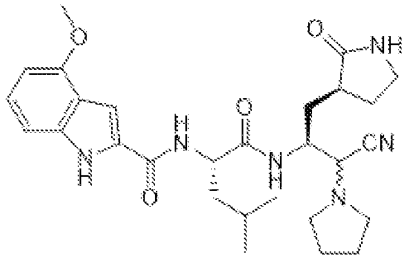

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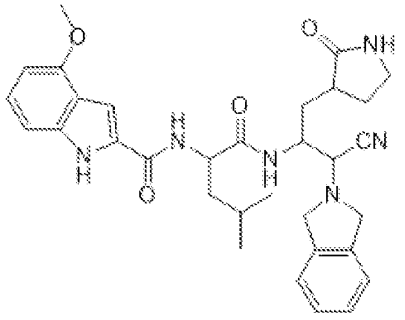

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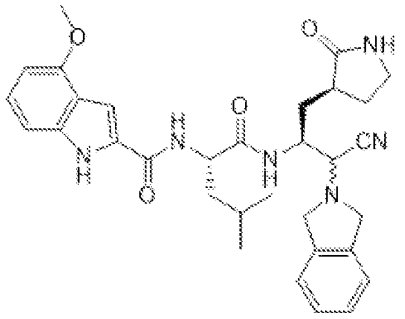

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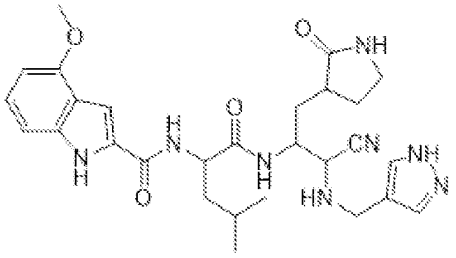

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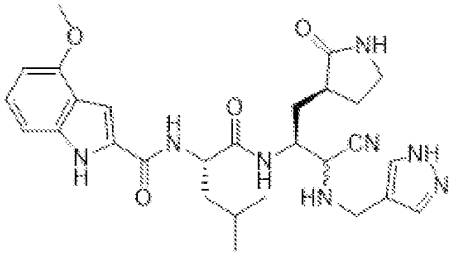

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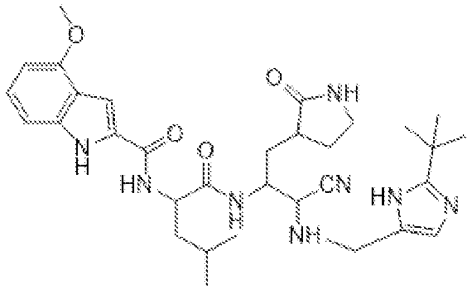

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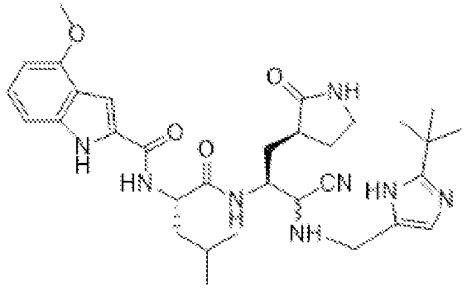

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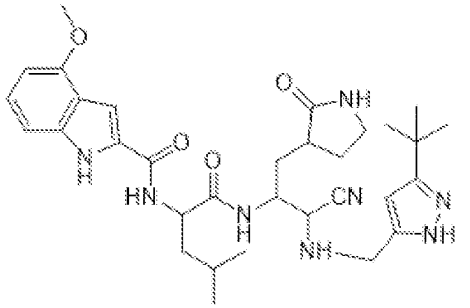

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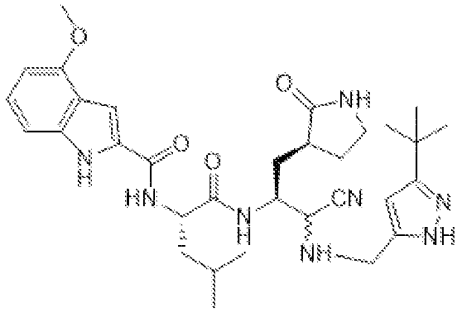

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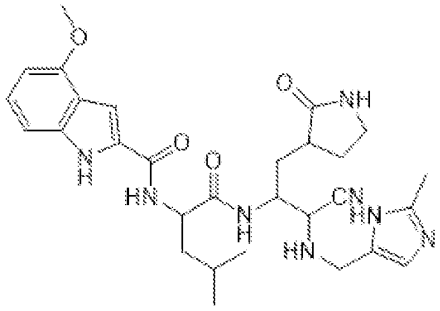

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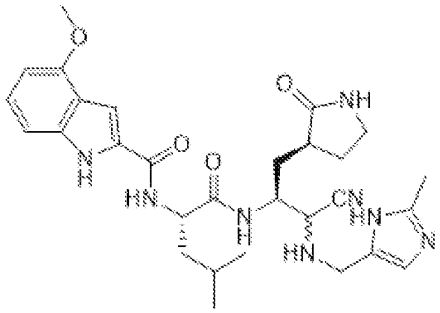

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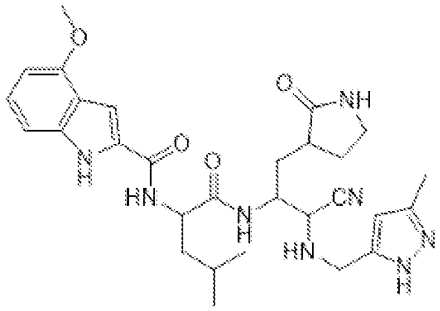

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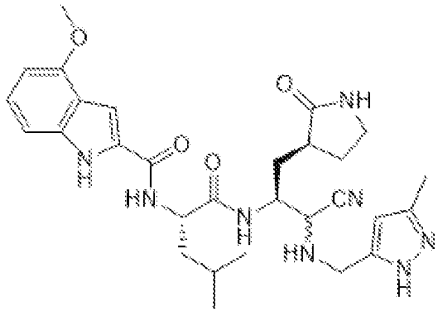

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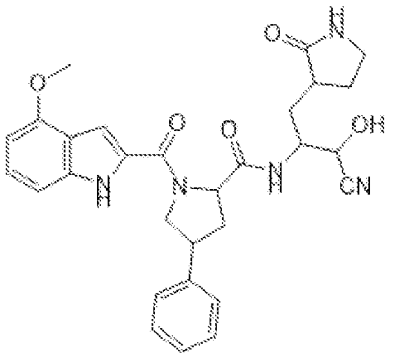

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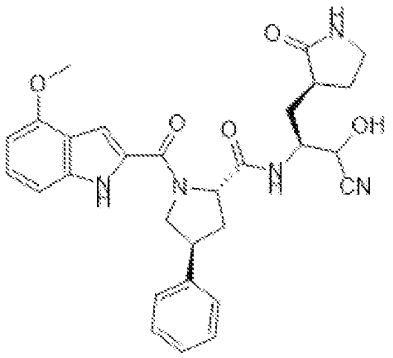

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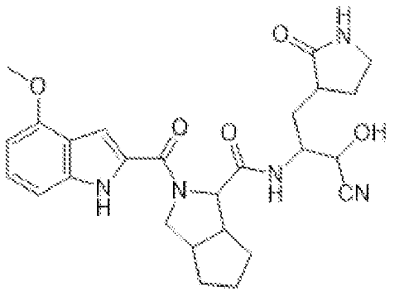

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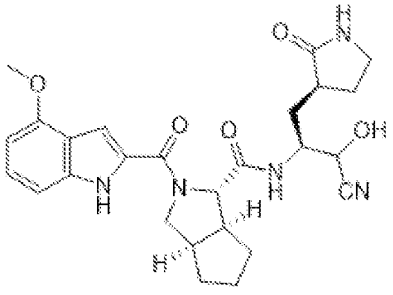

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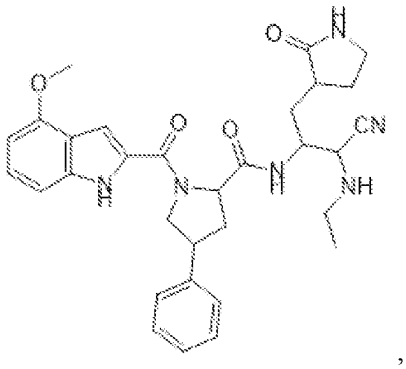

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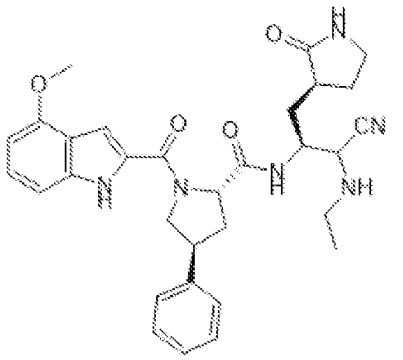

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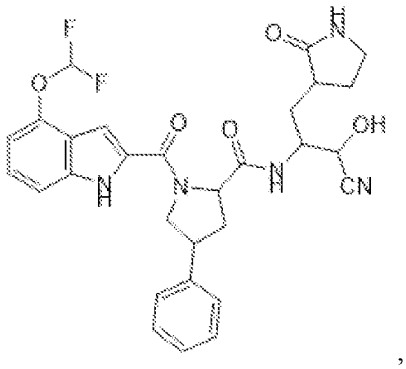

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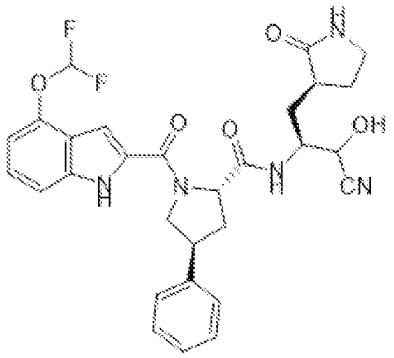
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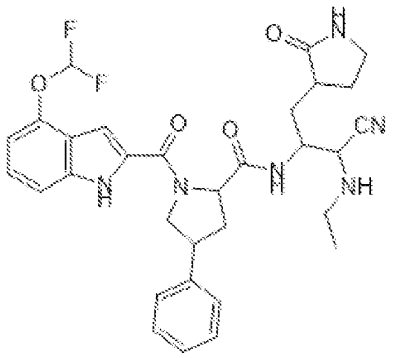


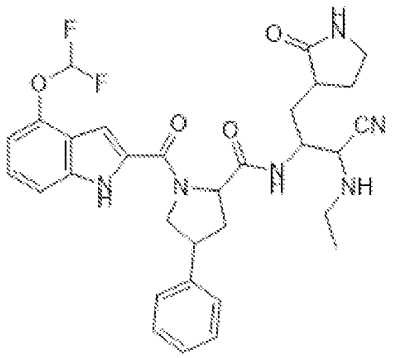
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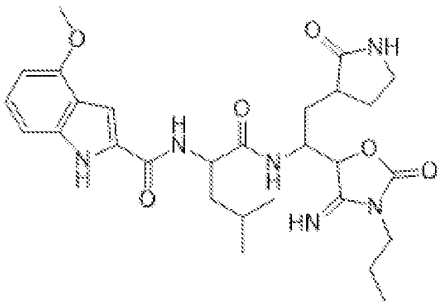


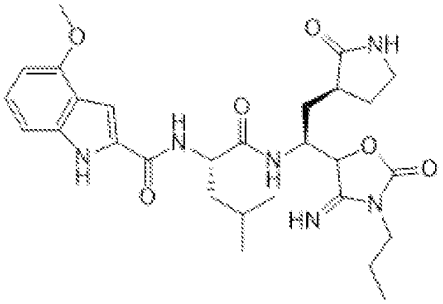
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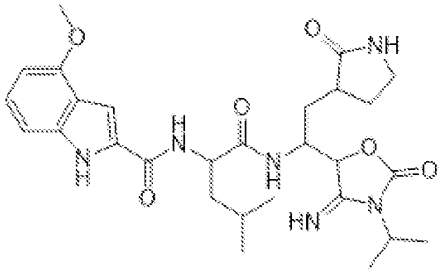

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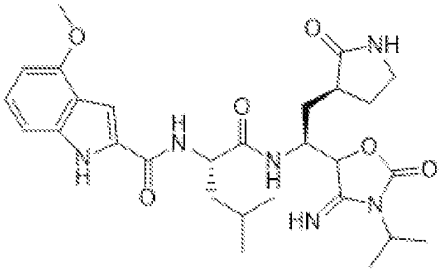

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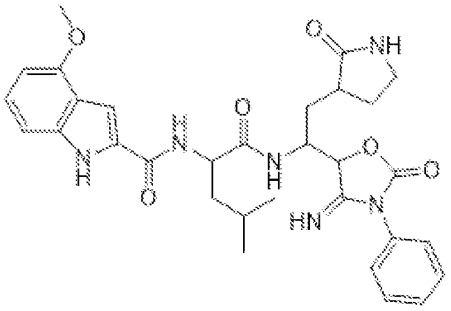

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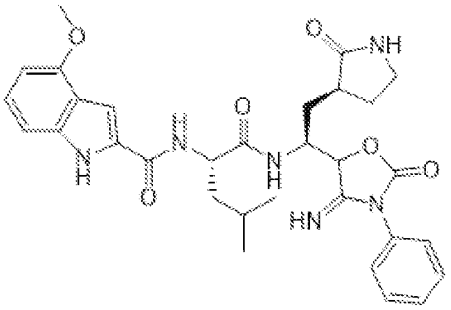

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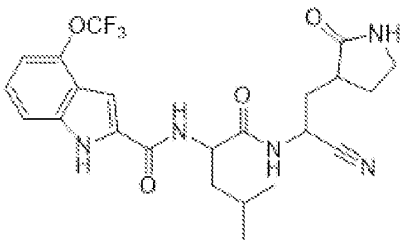

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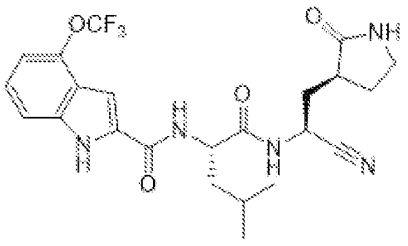

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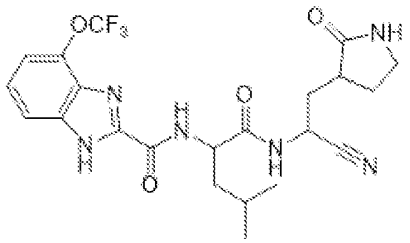

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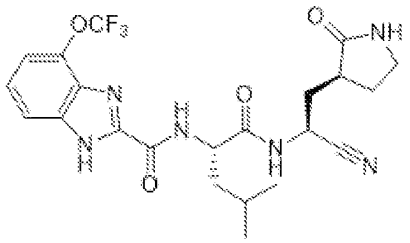

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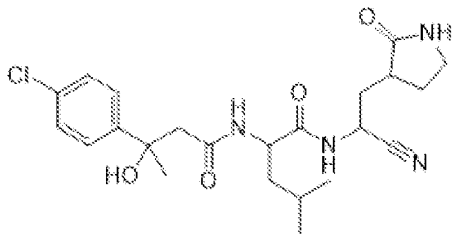

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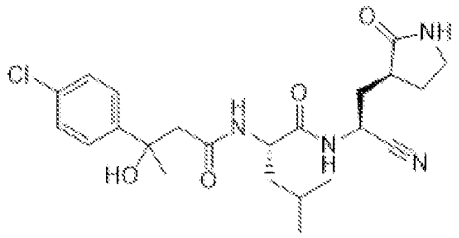

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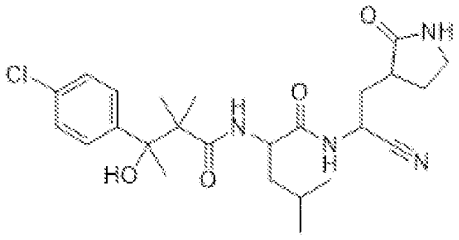

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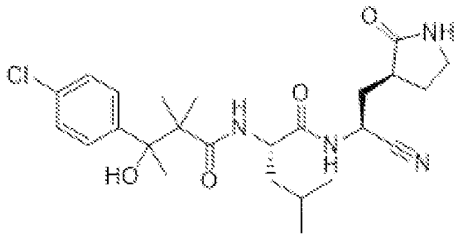

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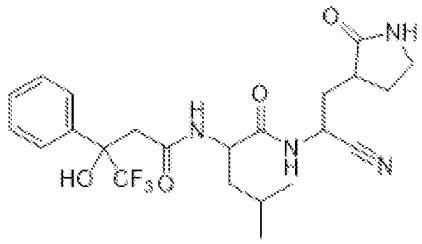

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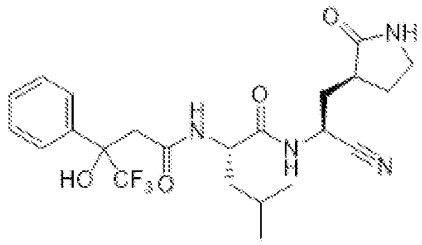

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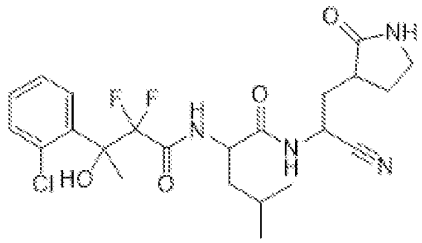

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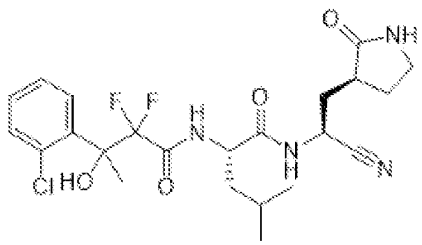

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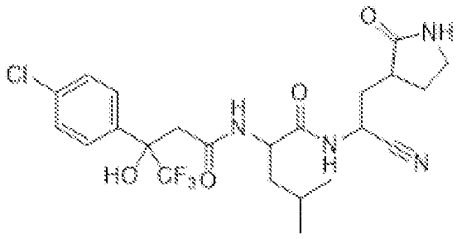

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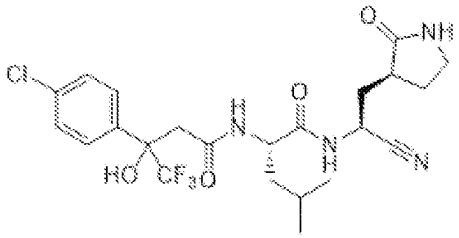

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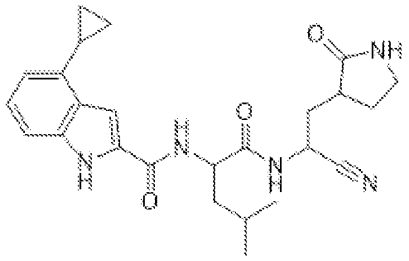

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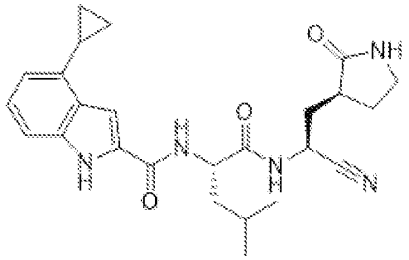

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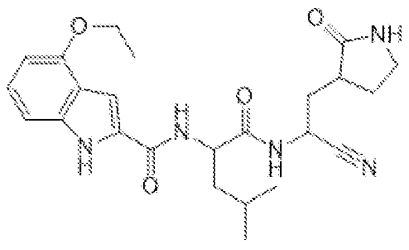

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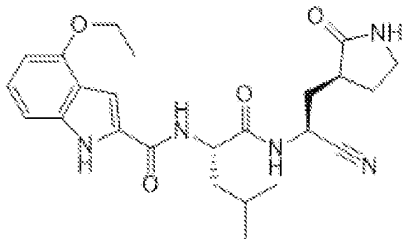

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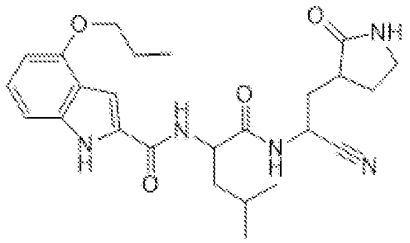

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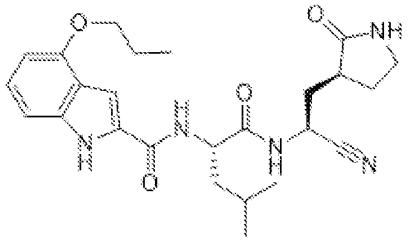

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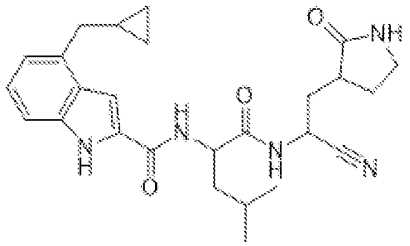

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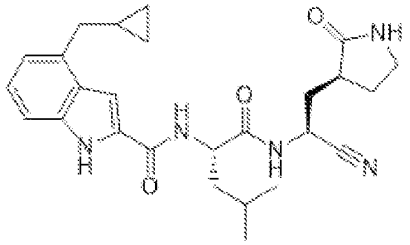

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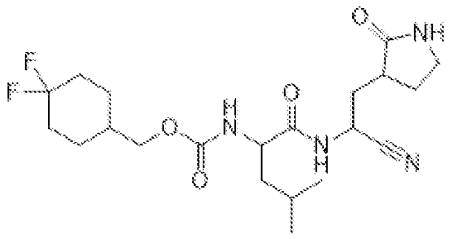

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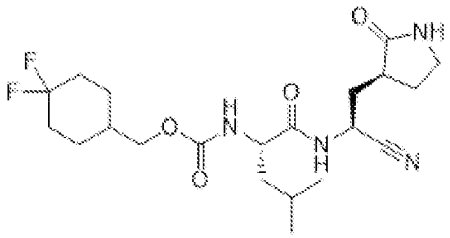

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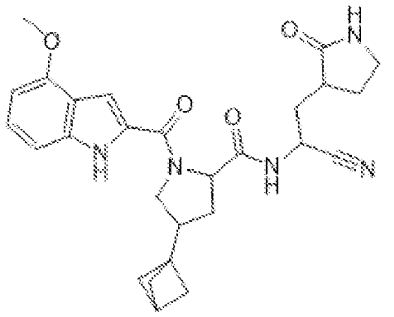

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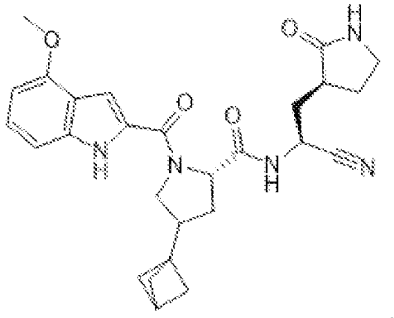
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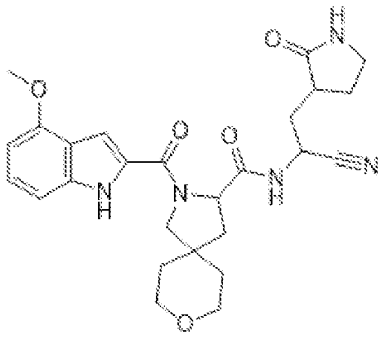
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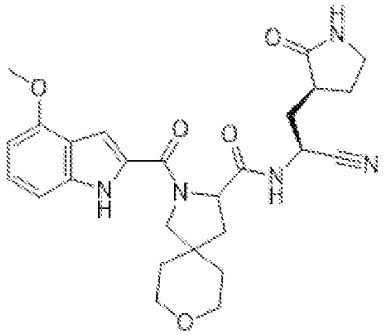


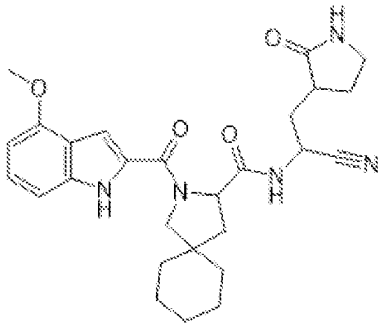
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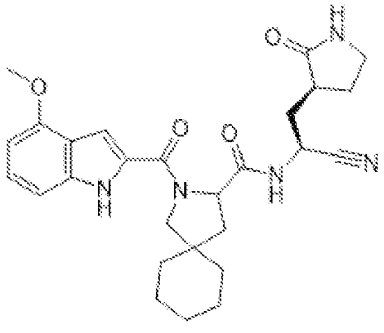


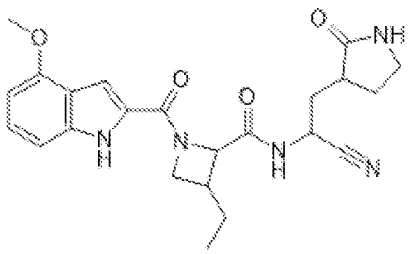
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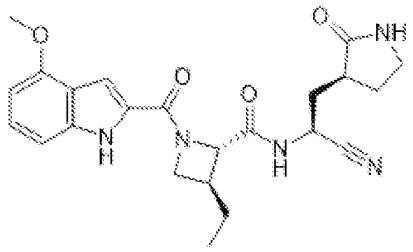

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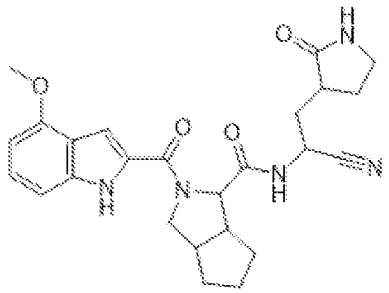

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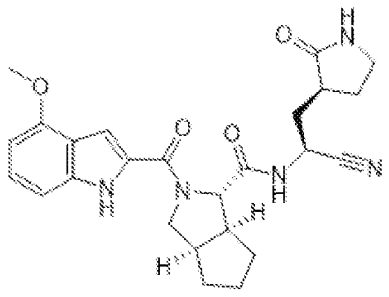

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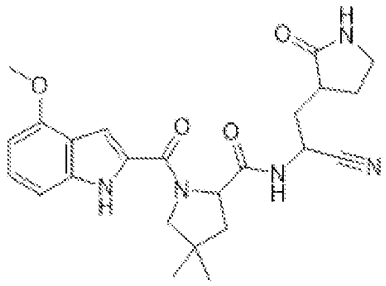

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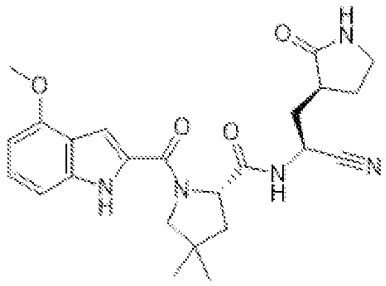

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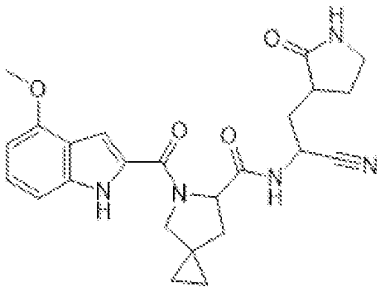

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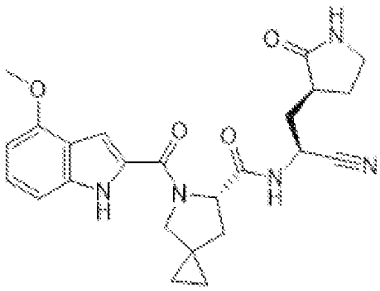

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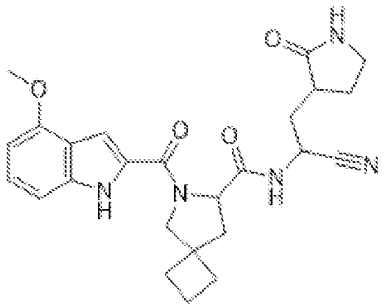

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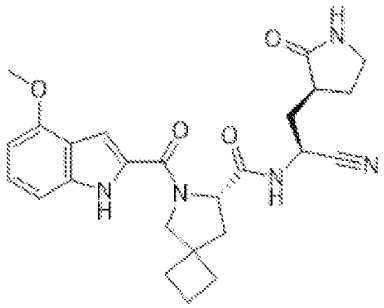

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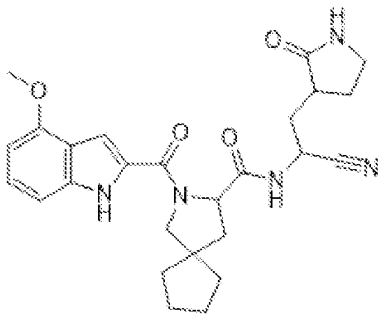

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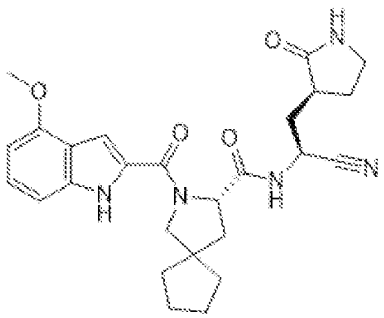

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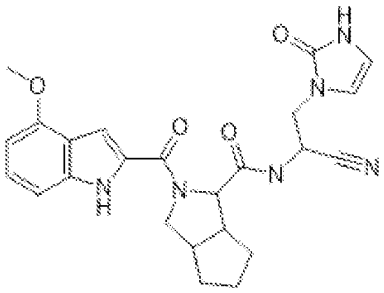

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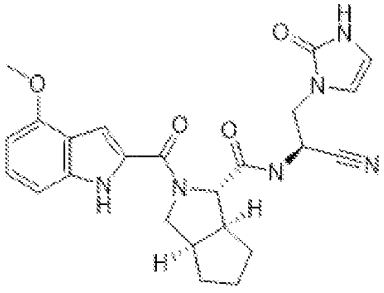

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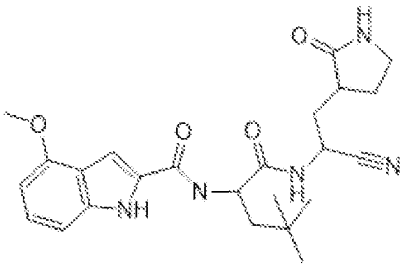

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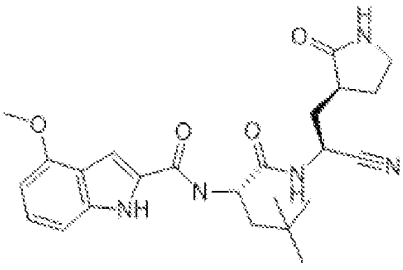

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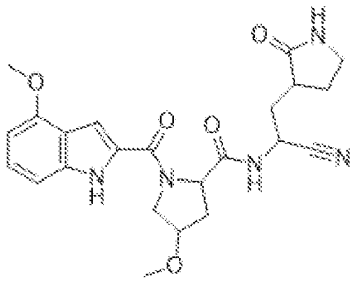

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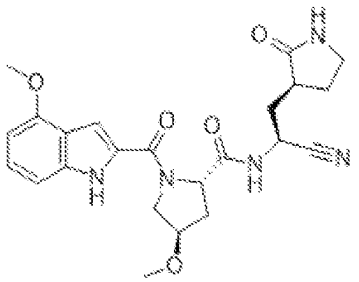

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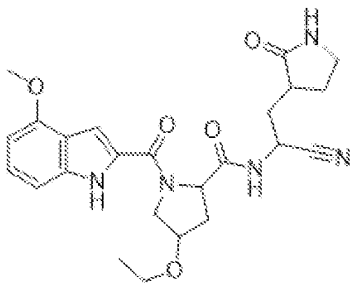

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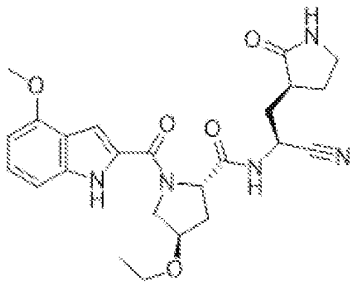

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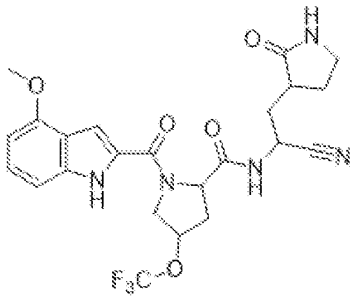

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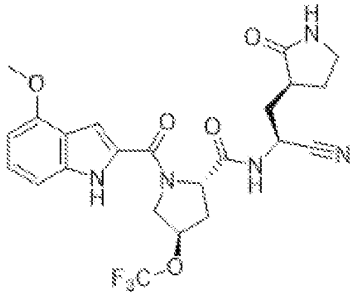

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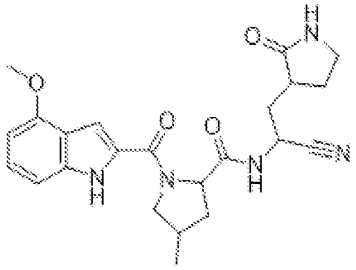

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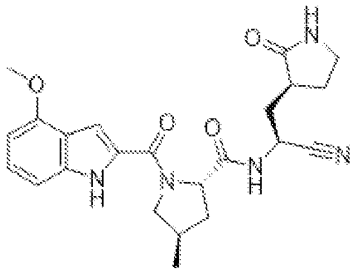

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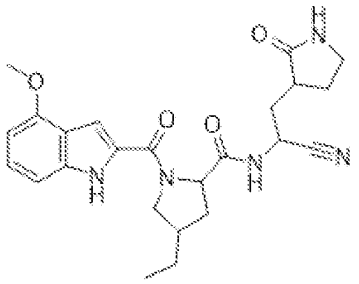

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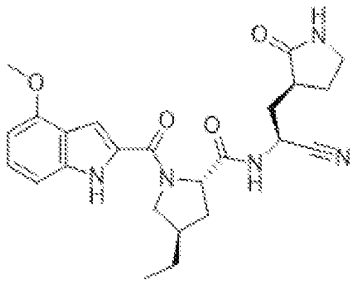

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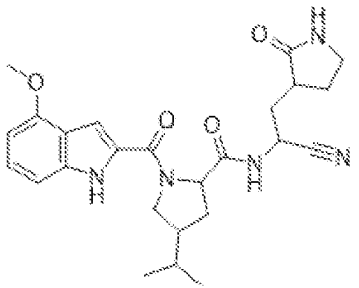

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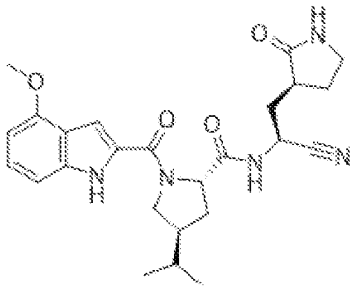

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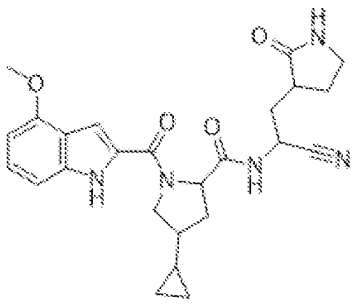

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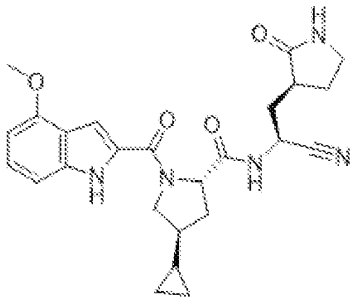

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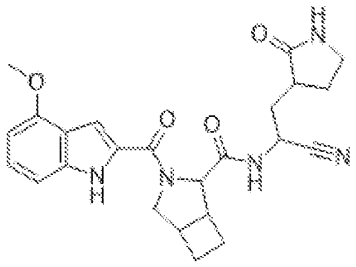

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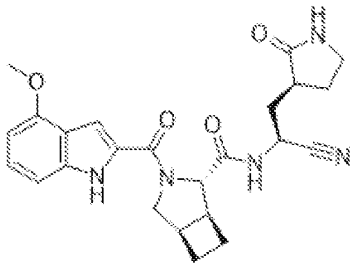

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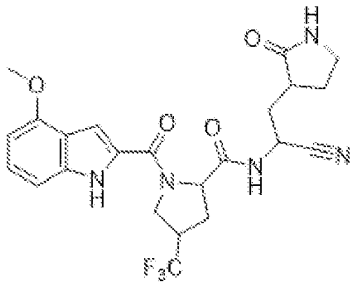

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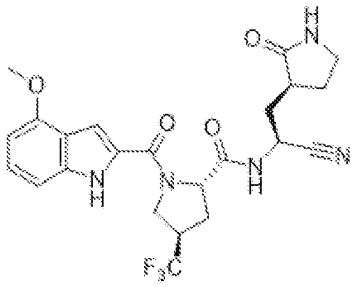

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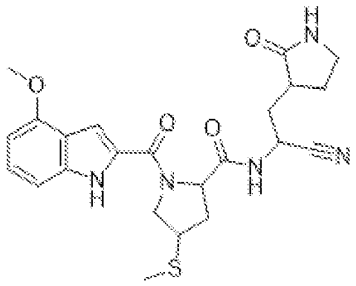

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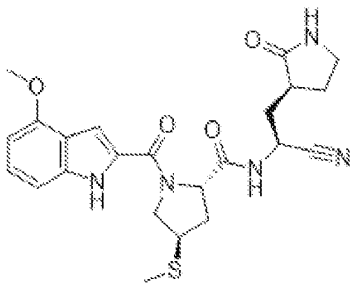

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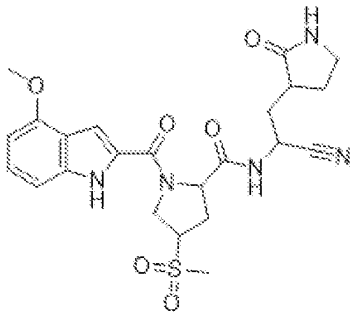

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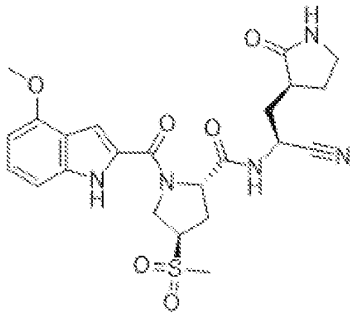

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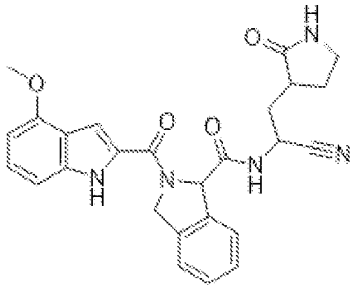

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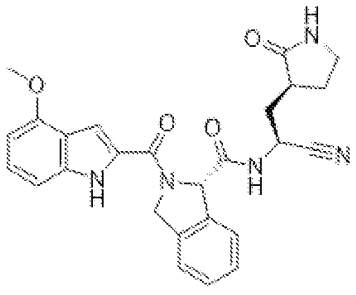

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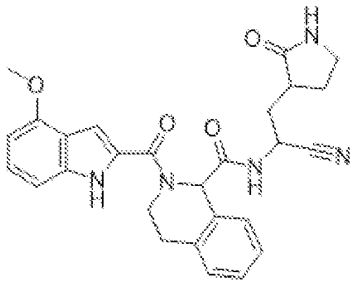

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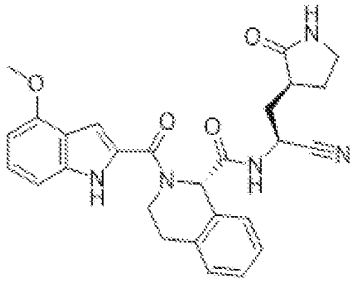

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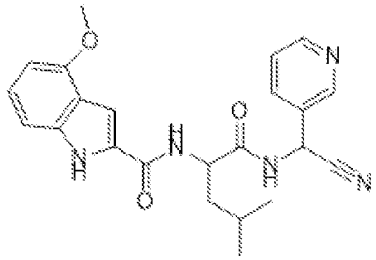

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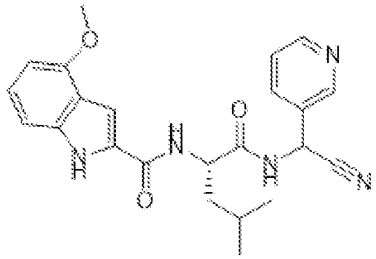

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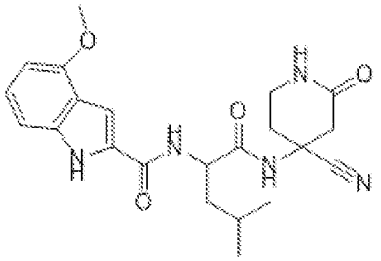

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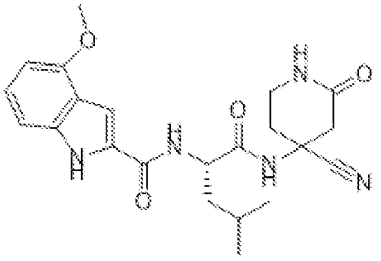

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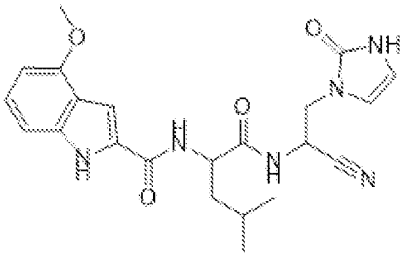

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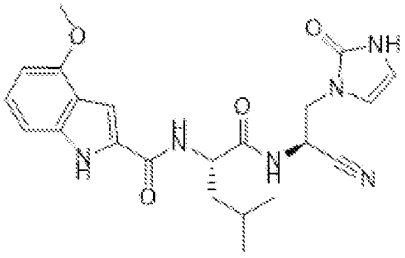

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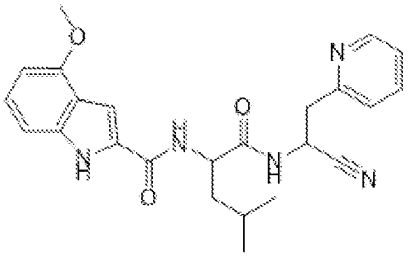

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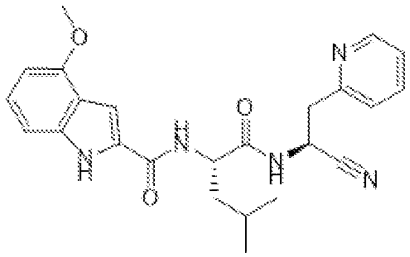

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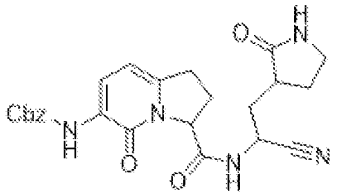

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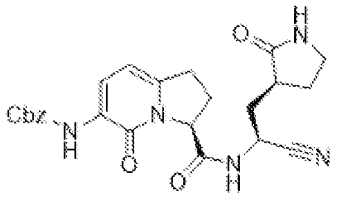

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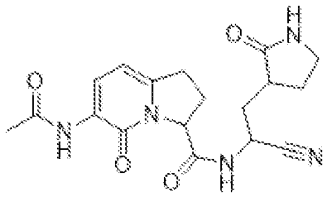

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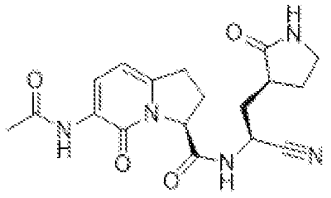

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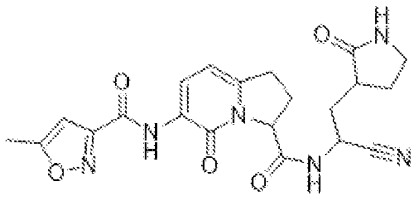

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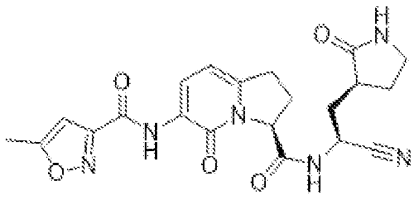

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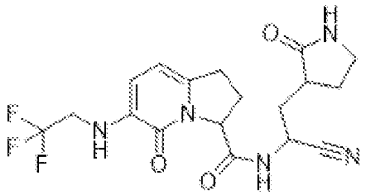

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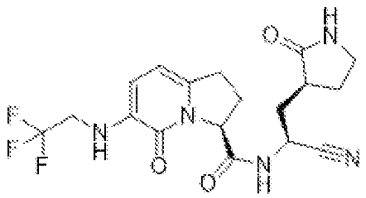

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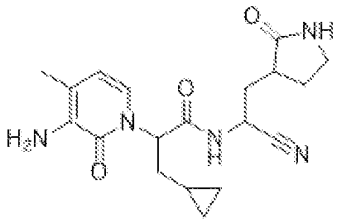

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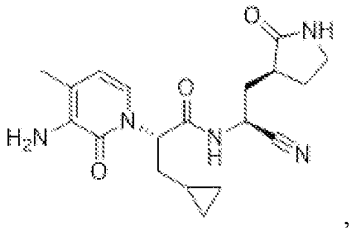

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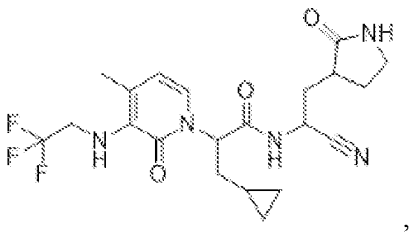

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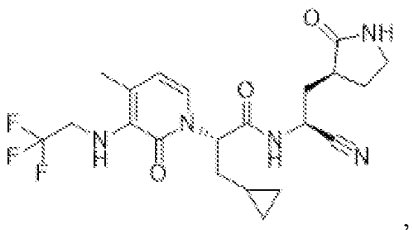

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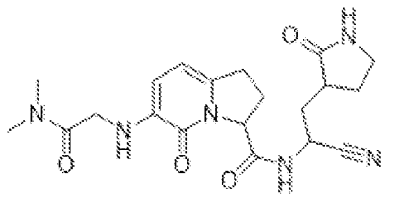

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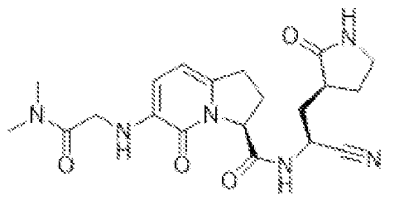

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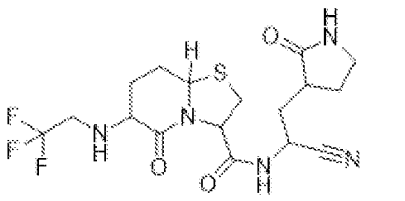

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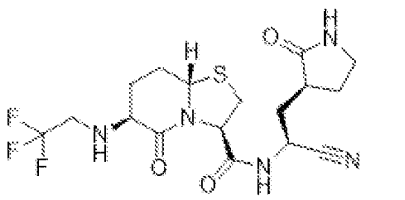

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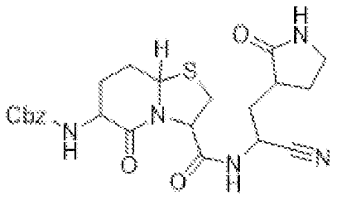

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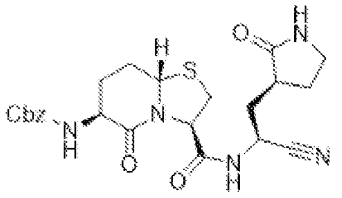

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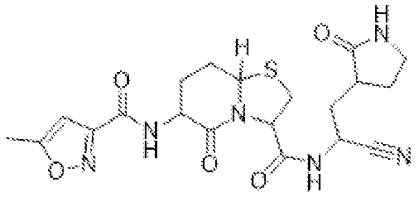

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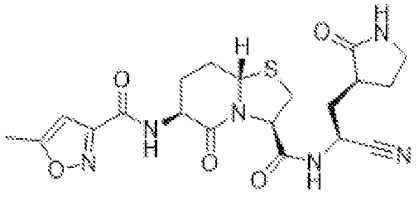
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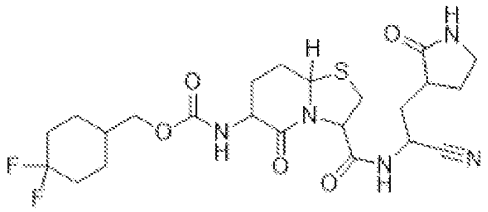
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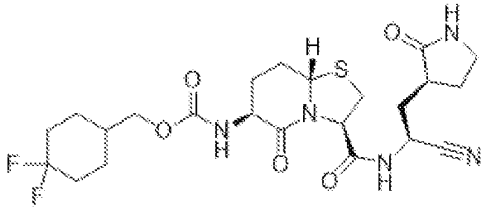
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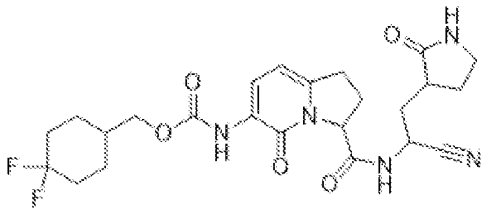
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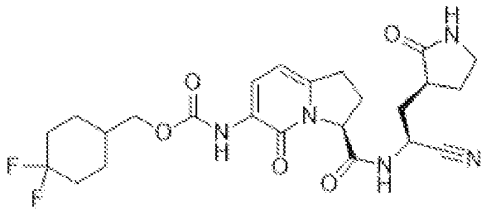

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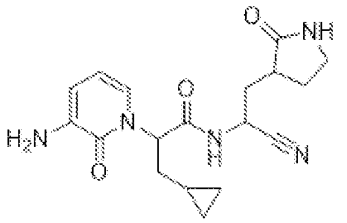
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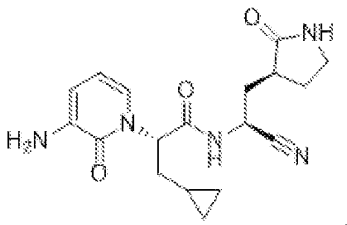

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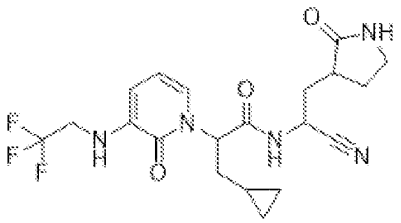
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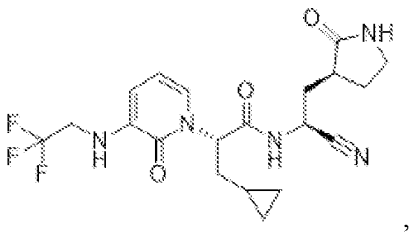

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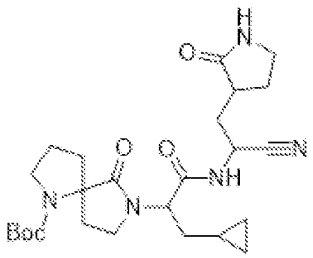

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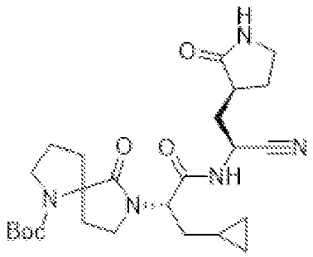

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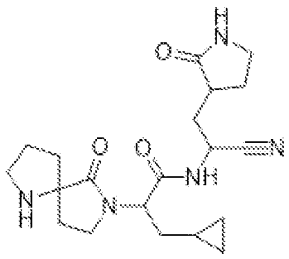

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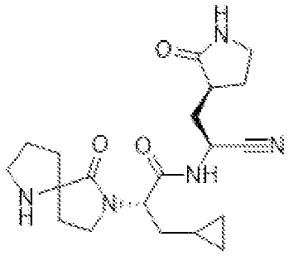

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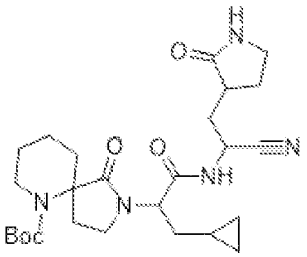

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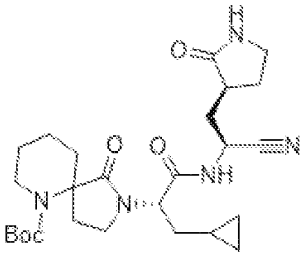

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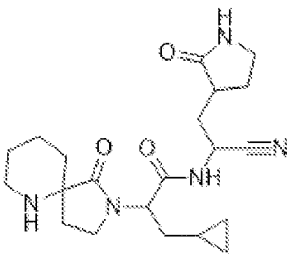

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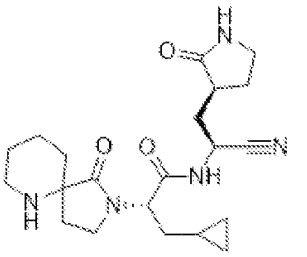

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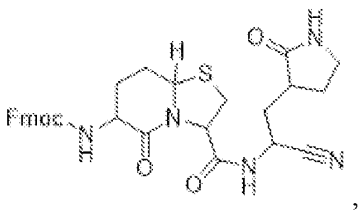

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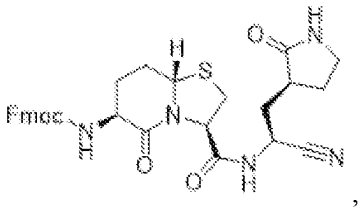

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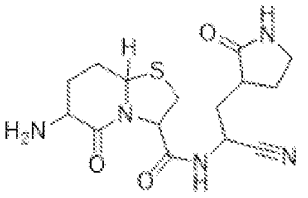

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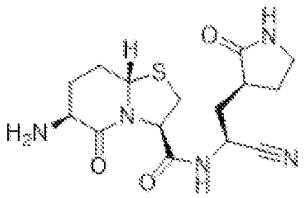

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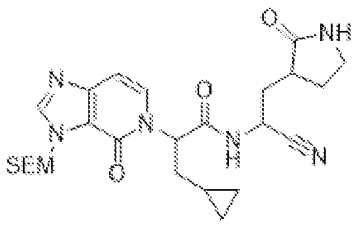
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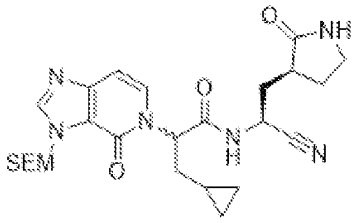
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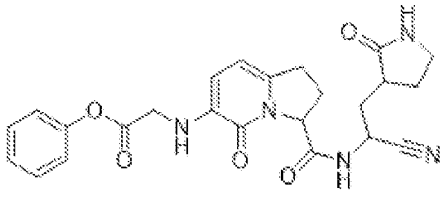
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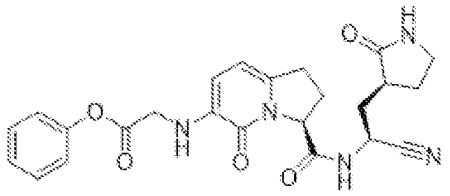
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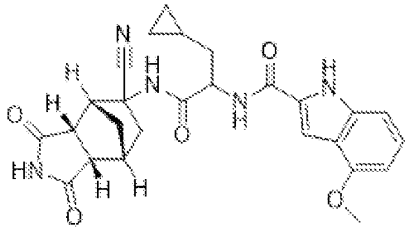

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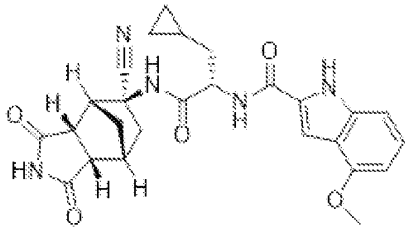
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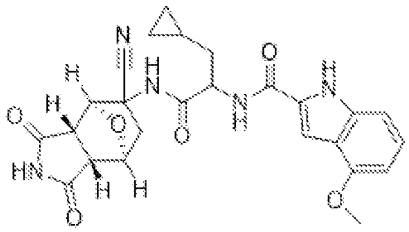

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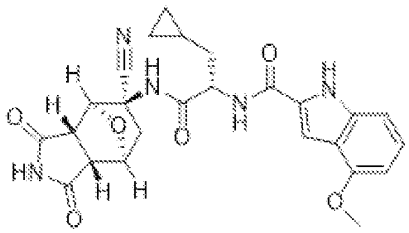
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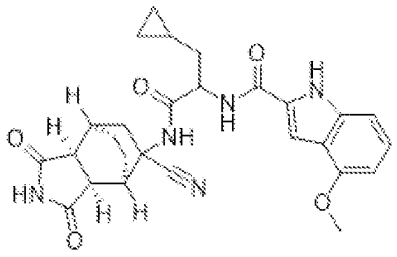

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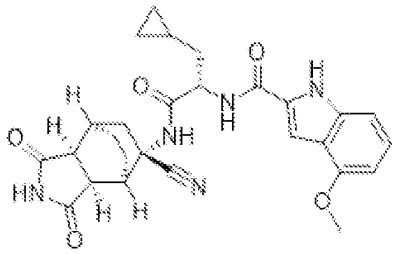

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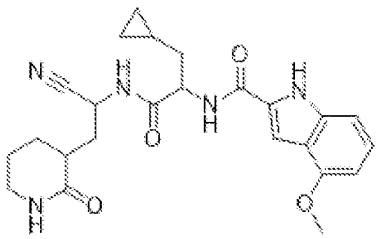

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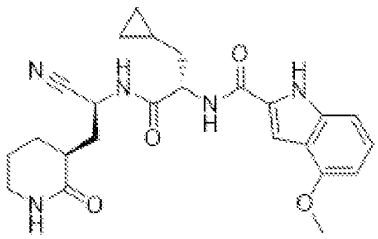

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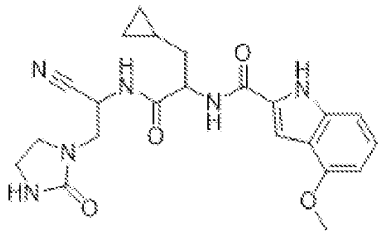

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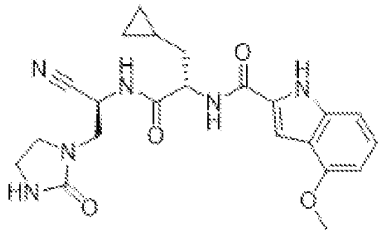

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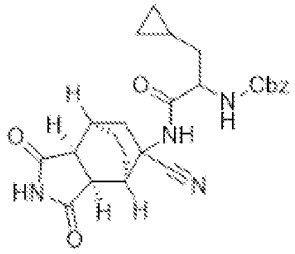

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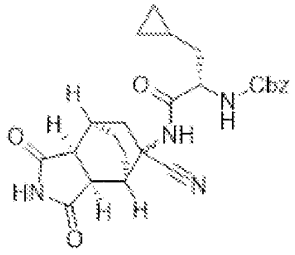

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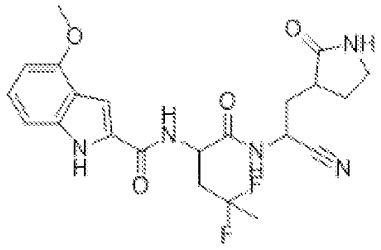

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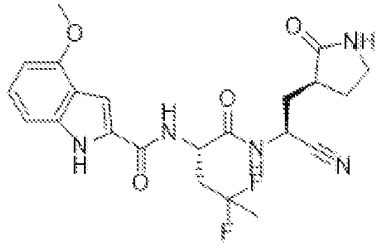

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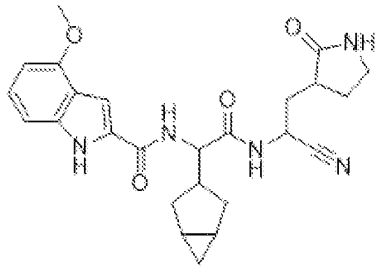

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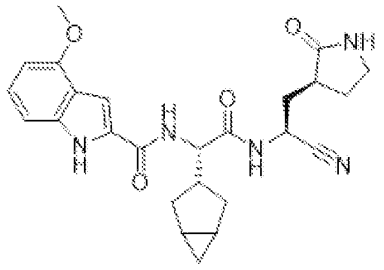

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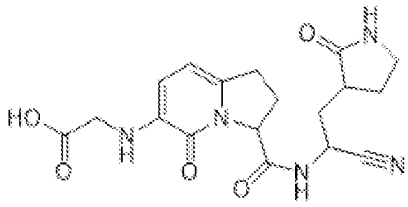

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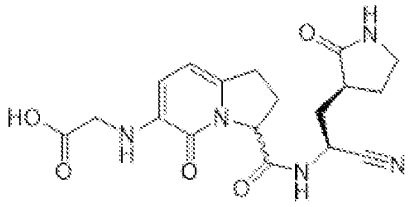

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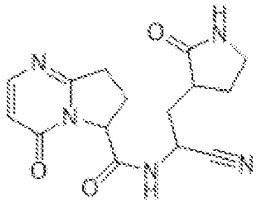

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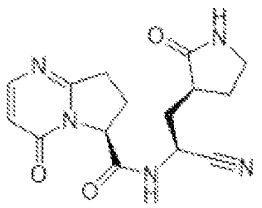

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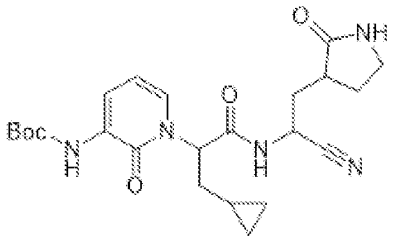

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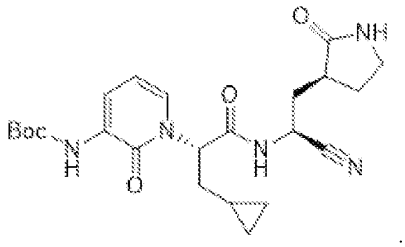

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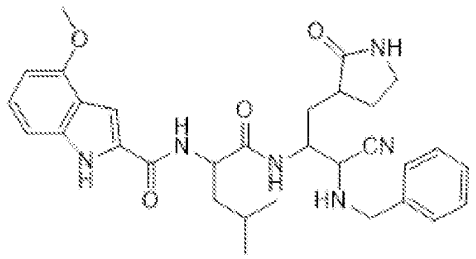

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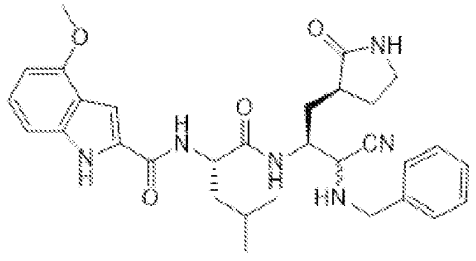

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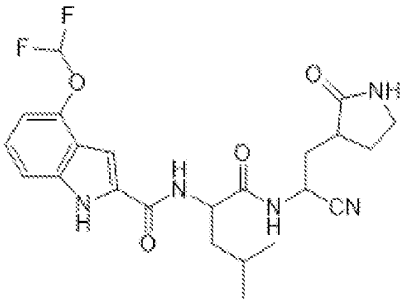

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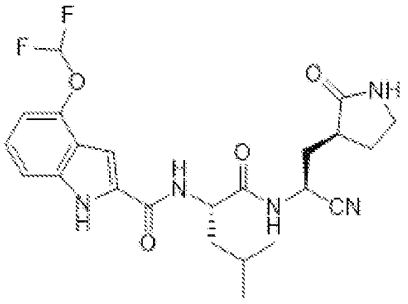

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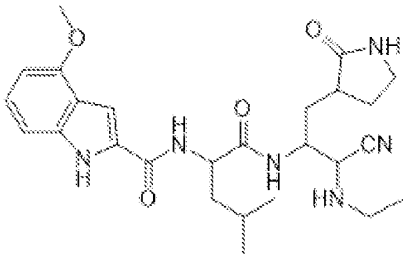

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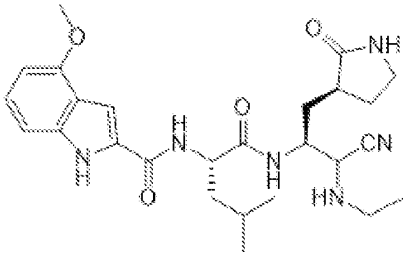

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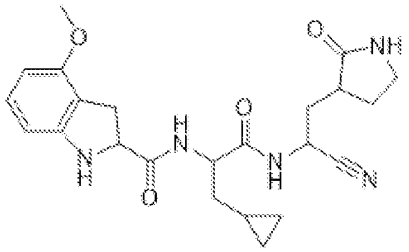

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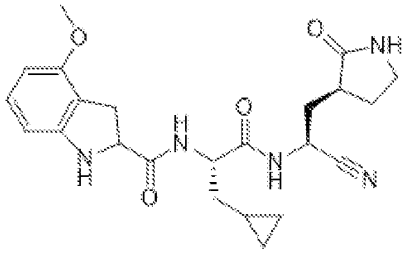

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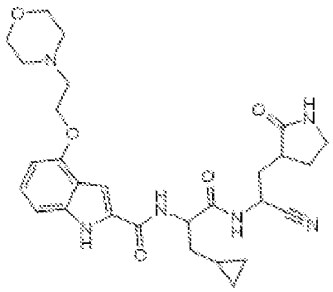

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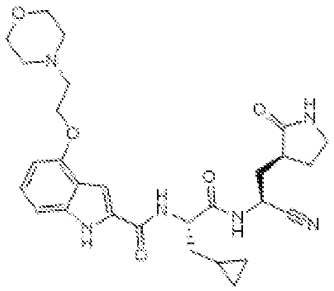

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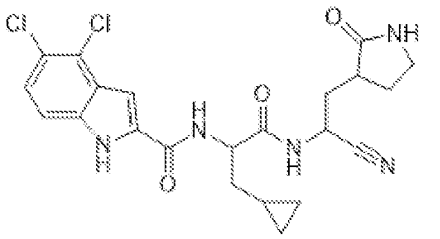

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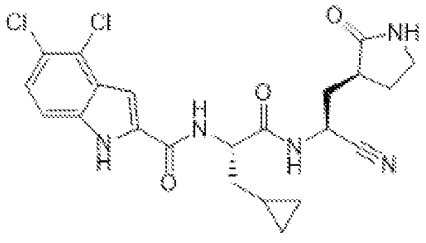

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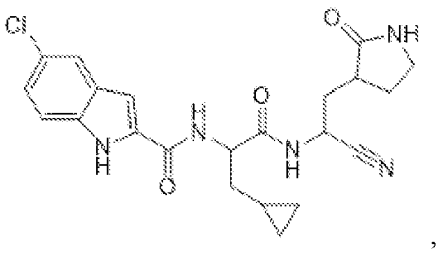

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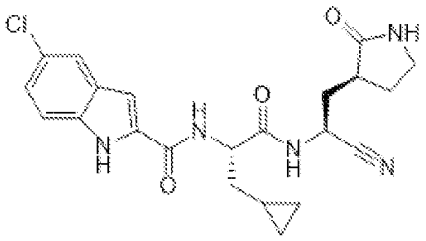
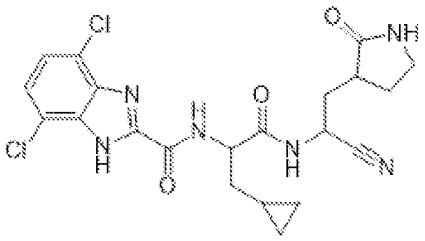
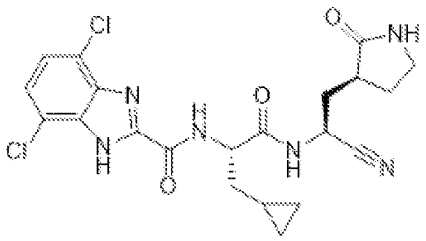
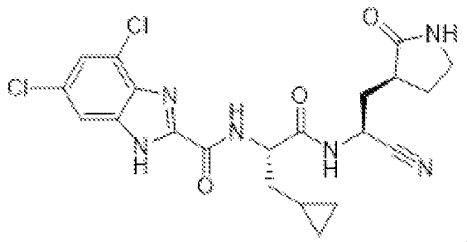
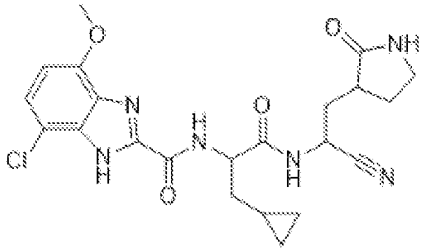
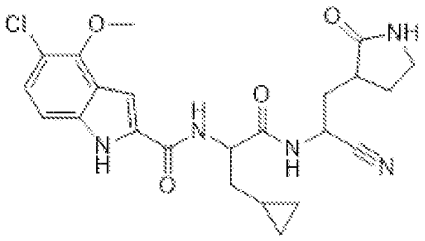
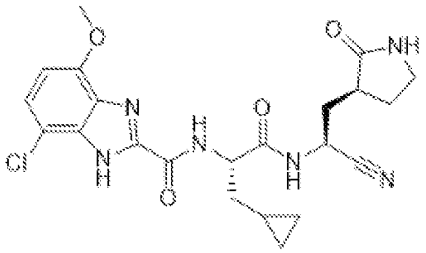
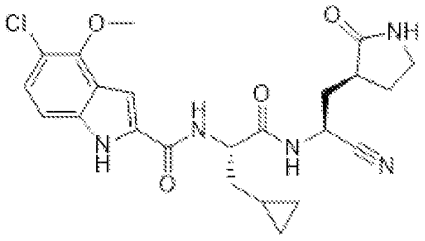
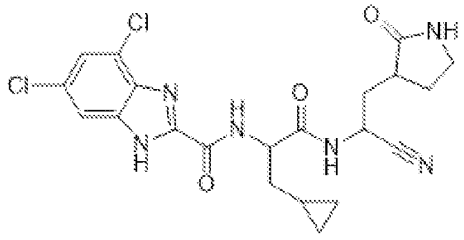
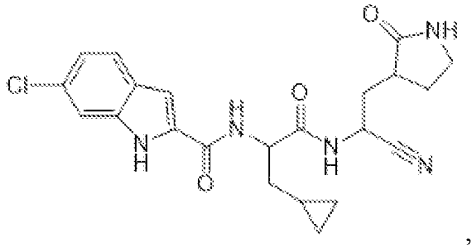

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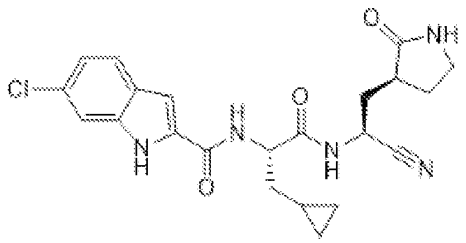

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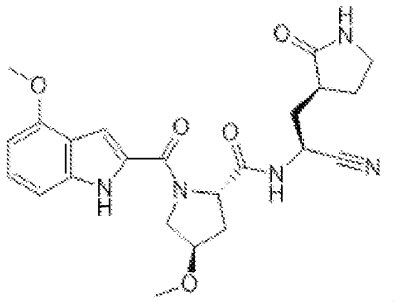

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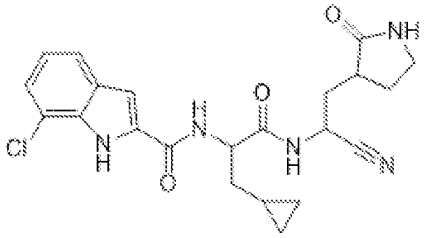

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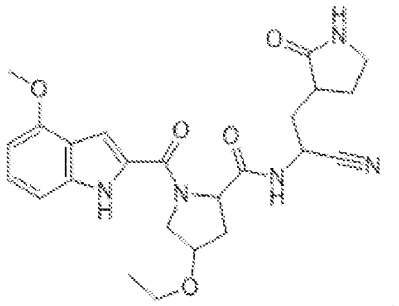
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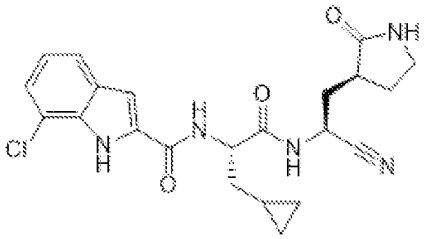
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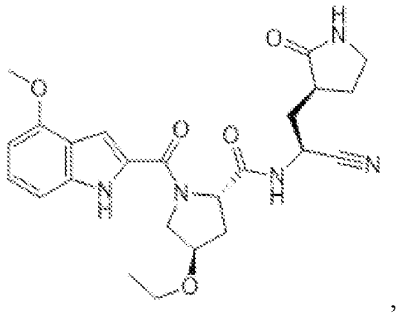
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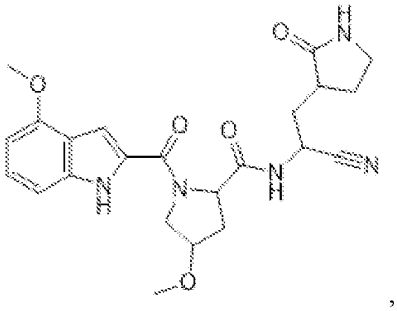
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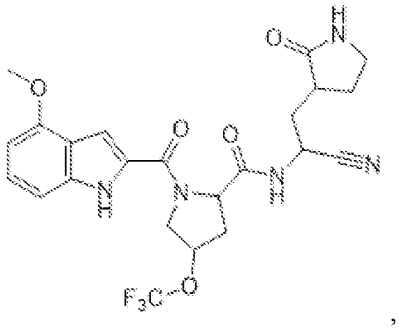
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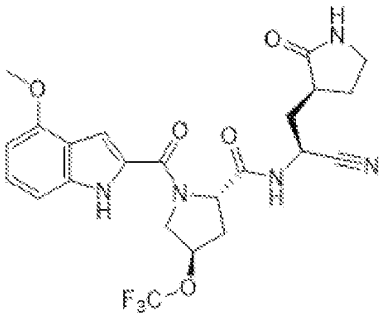
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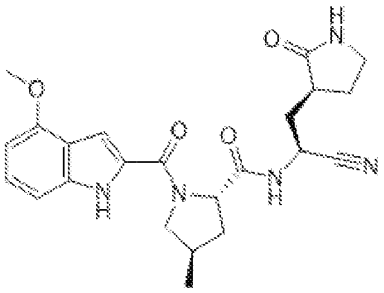
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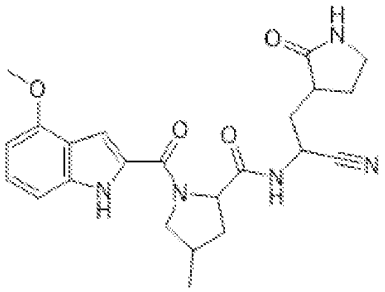
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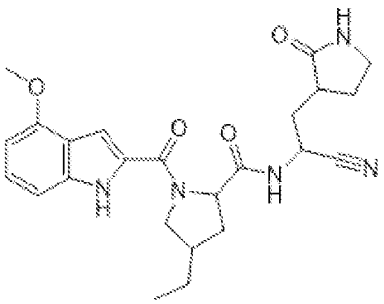
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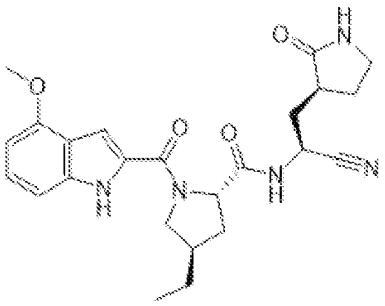
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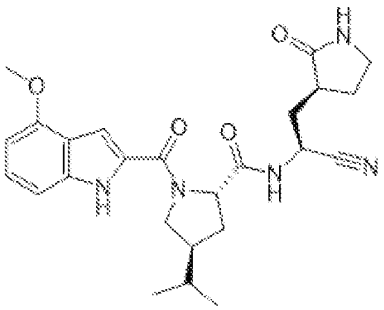
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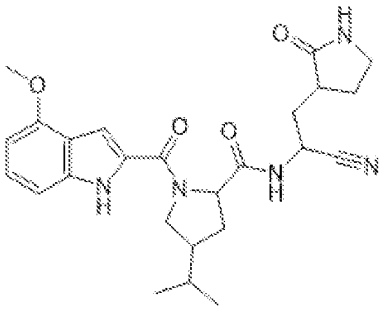
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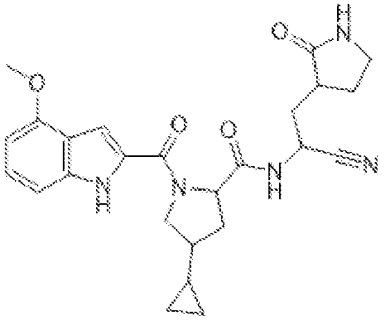
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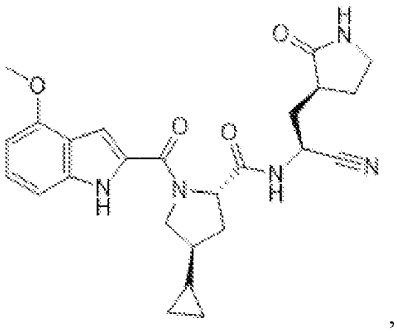
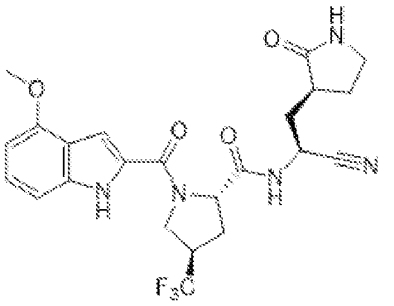
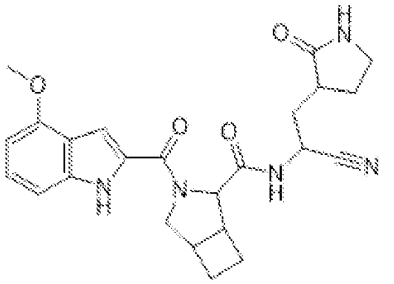
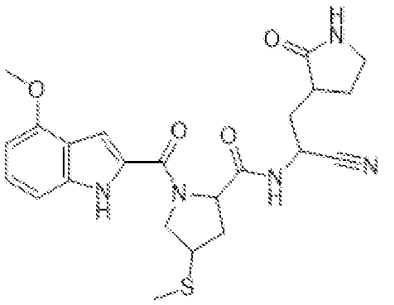
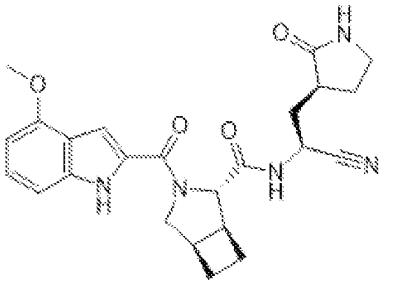
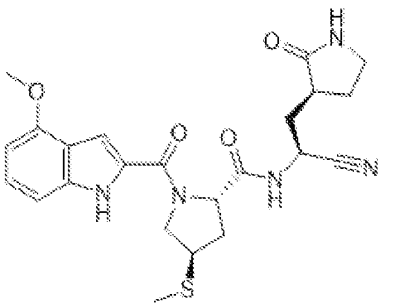
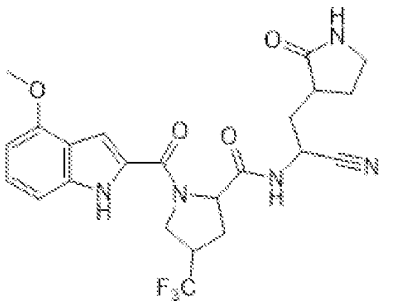
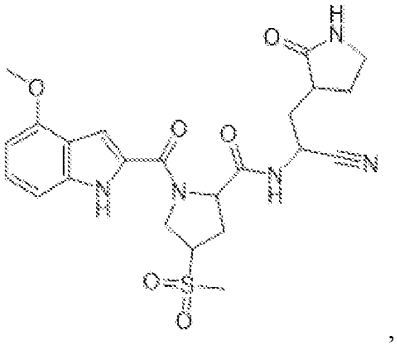
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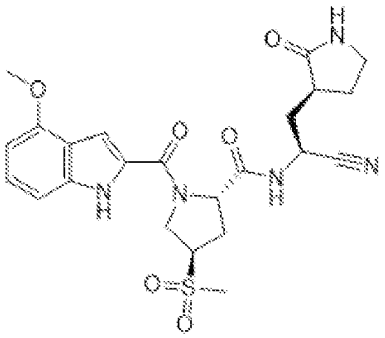
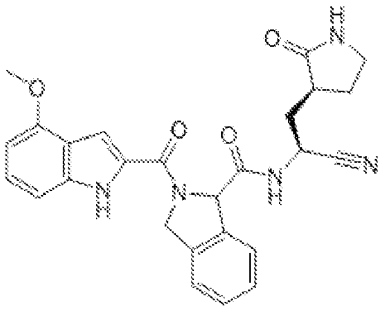
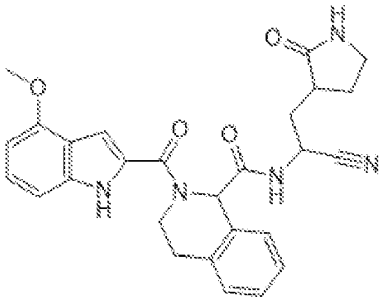
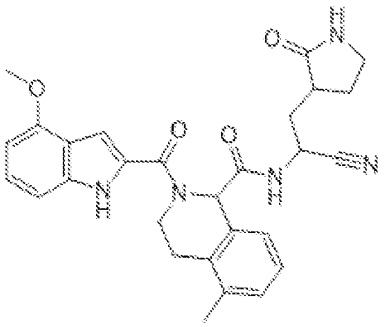
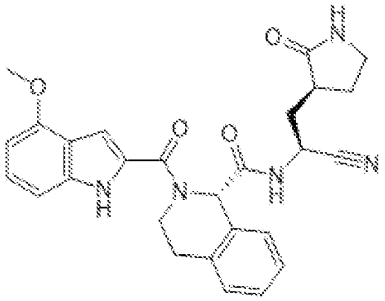
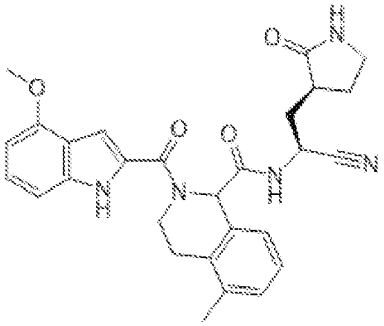
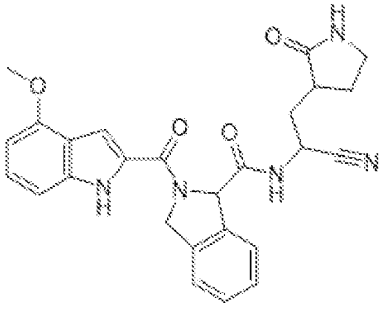
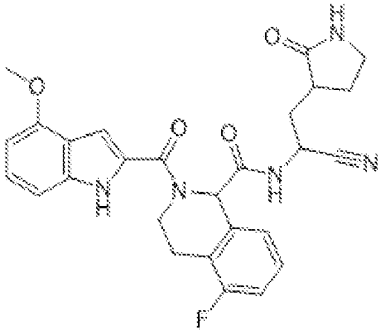


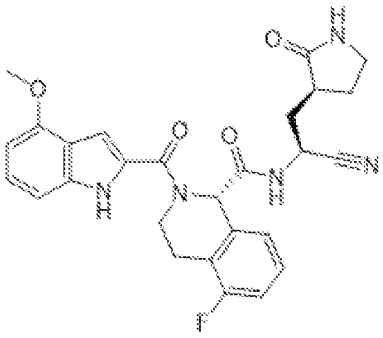
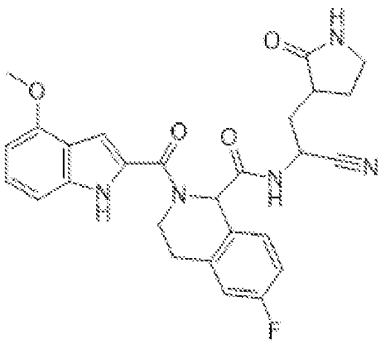
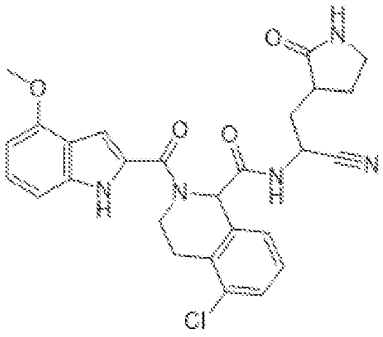
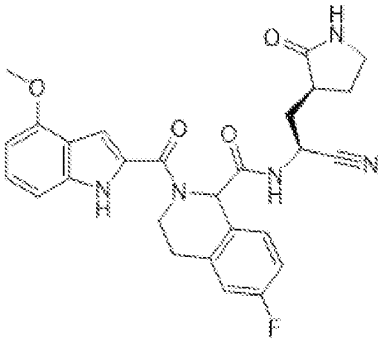
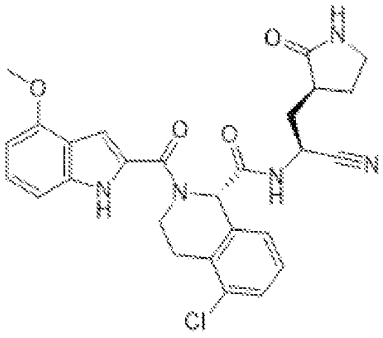
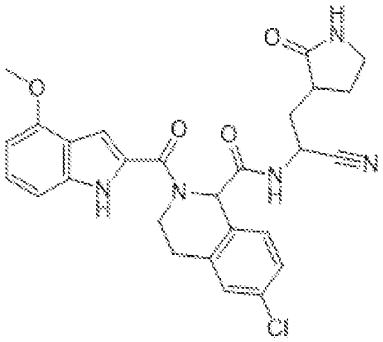
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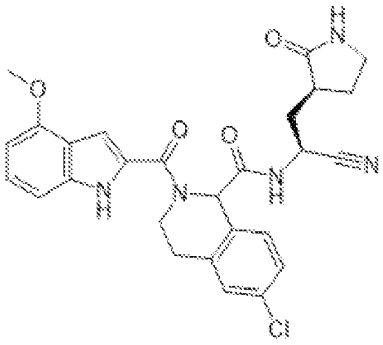


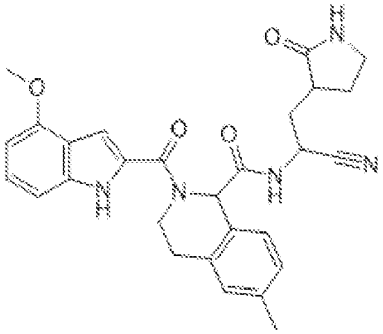
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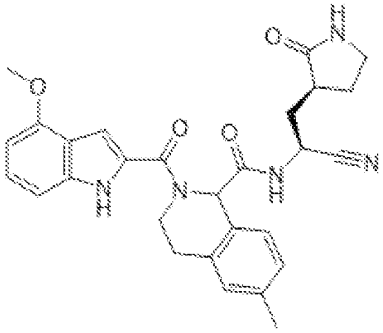

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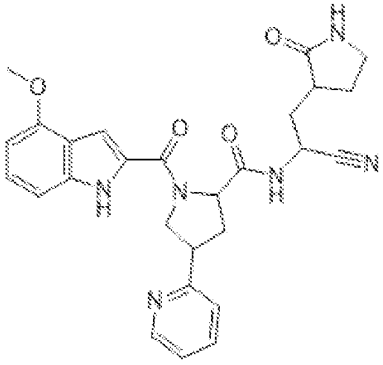

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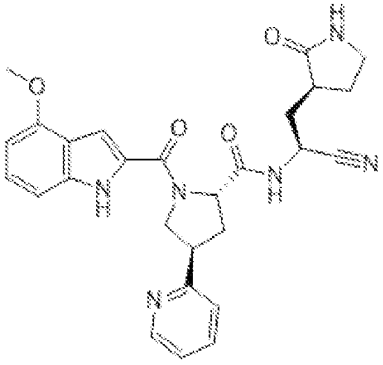

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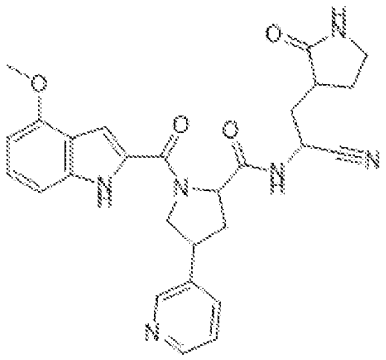

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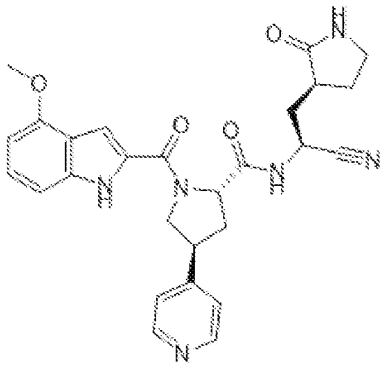

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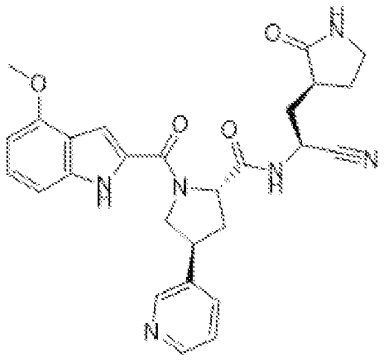

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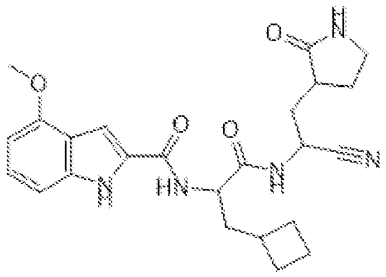

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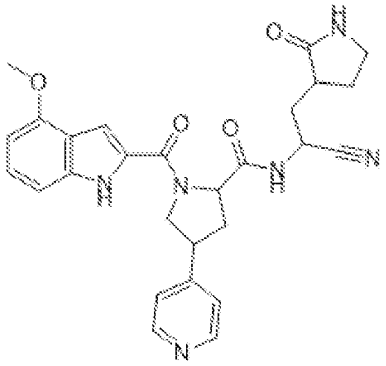

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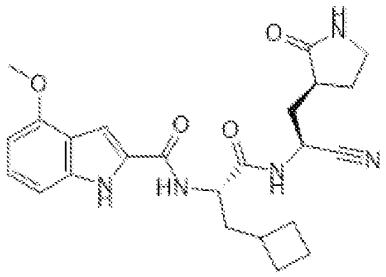

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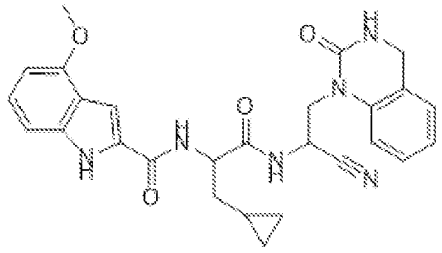

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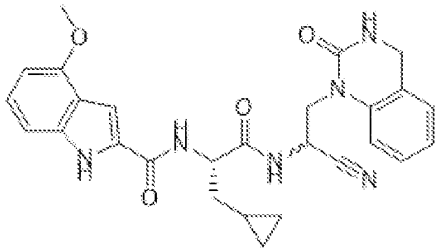

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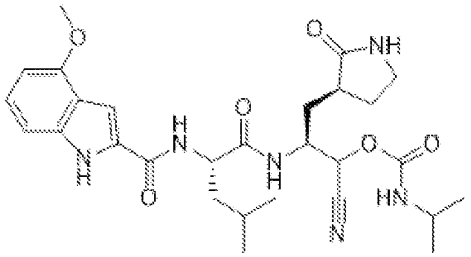

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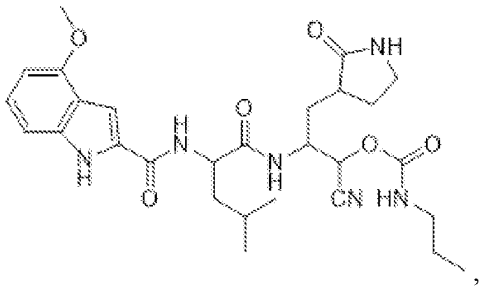

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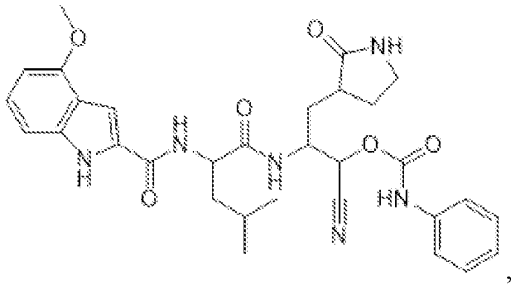
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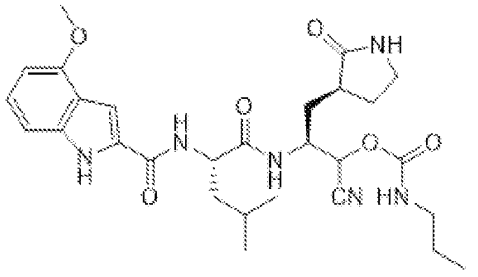
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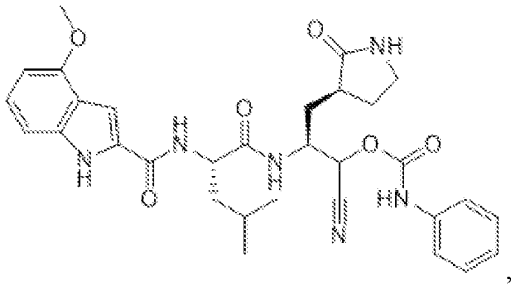
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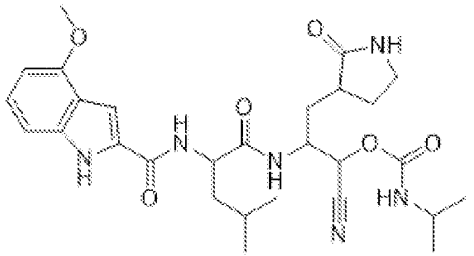
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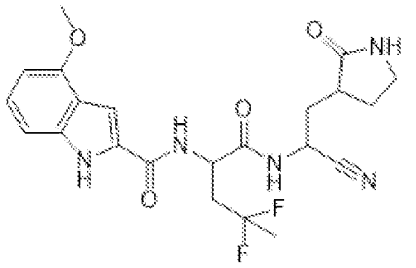
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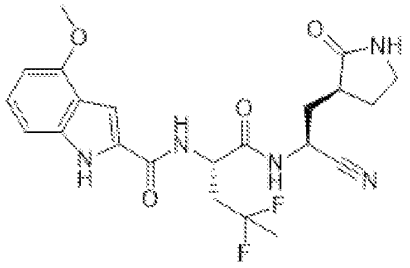
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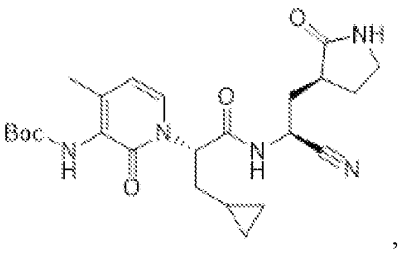


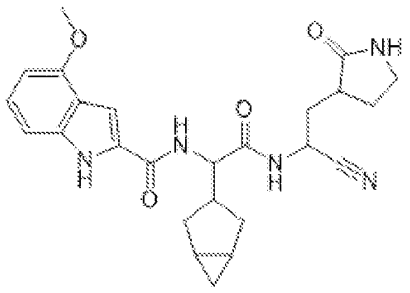
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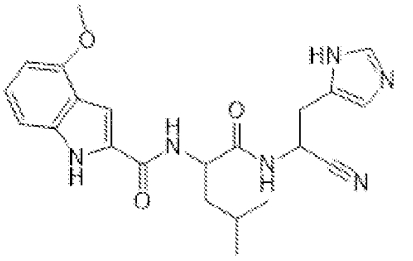


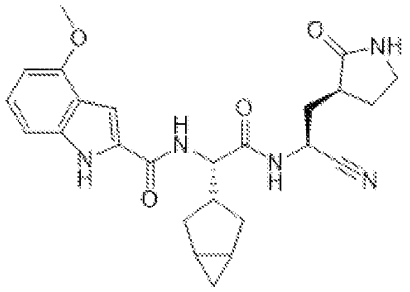
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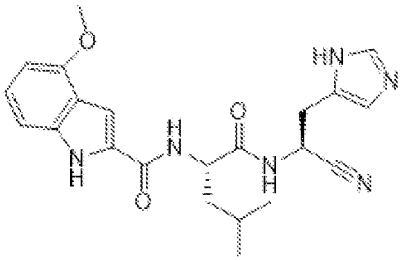

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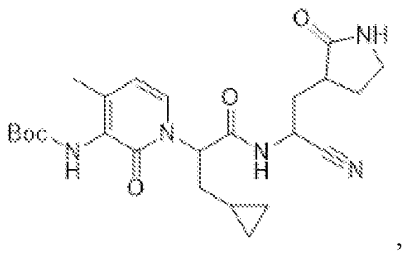

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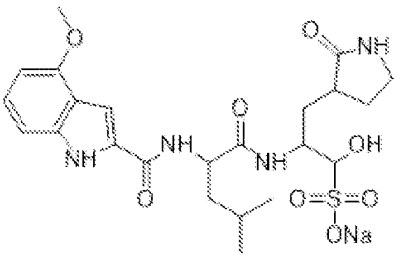

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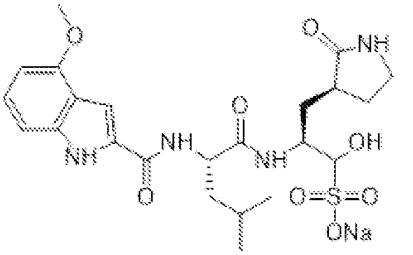

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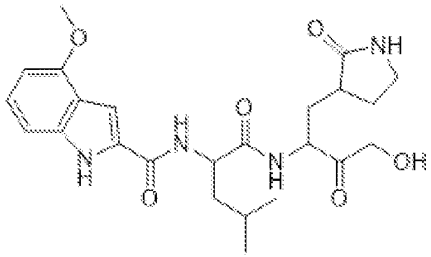
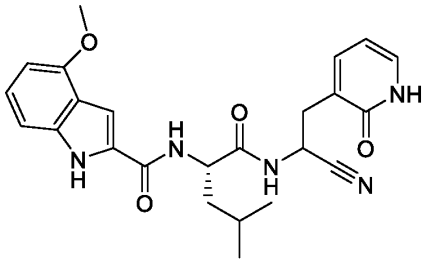
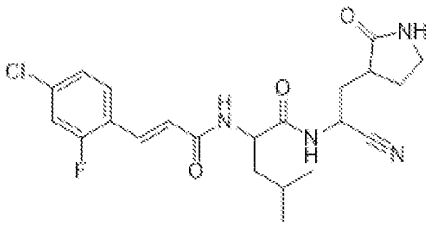
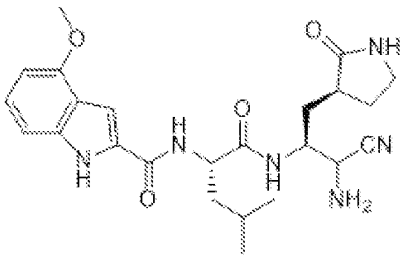
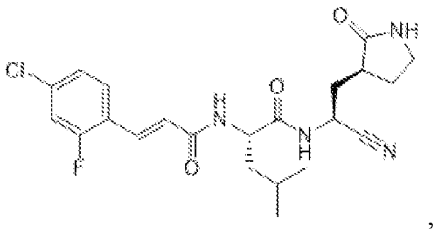
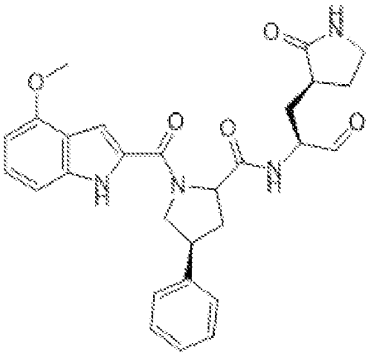
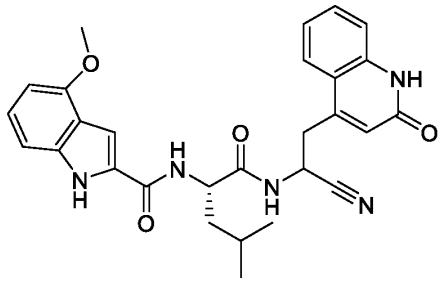
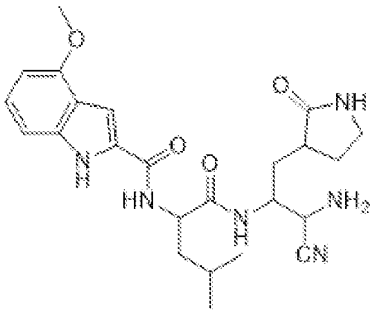

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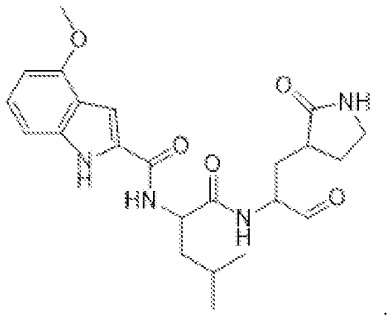

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17. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds of the embodiment.

18. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
19. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.
20. The viral infection is a coronavirus infection.
21. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).
22. The viral infection is SARS-CoV-2.
23. The viral infection is an arenavirus infection.

24. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.
25. The viral infection is an influenza infection.
26. The influenza is influenza H1N1, H3N2 or H5N1.
27. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of any compound of the embodiment to a patient suffering from the virus, and/or contacting an effective amount of any compound of the embodiment with a virally infected cell.
28. The method further comprises administering another therapeutic.
29. The method further comprises administering an additional anti-viral therapeutic.
30. The anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.
31. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin,

ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

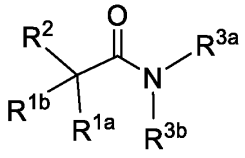
32. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.

33. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of any compound of the embodiment.
34. The compound is administered before viral exposure.
35. The compound is administered after viral exposure.

5. Contemplated Embodiment

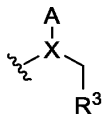
[0194] In another aspect, the compositions, compounds and methods of the present disclosure may be described in another embodiment as follows:

1. A protease inhibitor compound represented by:



Formula II,

wherein:



R^{3a} is selected from and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, –CH_2CF_3, CF_3, –O-CF_3, –O-CHF_2, –S-CH_3, –$S(O)_2$-CH_3, –NH_2, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –$NHC(O)R^B$, –$NHC(O)OR^B$, –NHC(O)O-(C_1-C_8alkyl)-R^B, –$N(R^y)_2$, –$N(R^y)$(C_1-C_8alkyl)C(O)O-phenyl, –$N(R^y)$(C_1-C_8alkyl)$C(O)N(R^y)_2$, –$NHC(O)O(C_1$-C_8alkyl)R^B, –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocycle), –C(O)-O-(4-10 membered heterocycle), –$C(O)OC(CH_3)_3$, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), –

(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the R^B, alkyl, heterocycle, heteroaryl, or aryl may optionally be substituted by one, two or three substituents of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl or oxo;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, –O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, $–OCHF_2$, $–OCF_3$, –O-(C_1-C_8alkyl), $–C(O)O(CH_3)$, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, $–N(R^y)(C_1$-C_8alkyl)$C(O)N(R^y)_2$, $–N(R^y)(C_1$-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo, halogen and C_1-C_8alkyl;

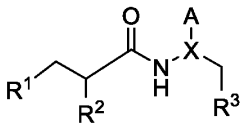
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, $–CH_2CF_3$, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH;

A is a warhead;

X is selected from the group consisting of $C(R^{xy})$ and N, wherein R^{xy} is selected from the group consisting of H, D, -OH, $-NH_2$, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy; and

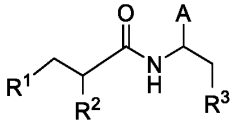
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

2. The compound is represented by:

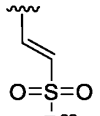
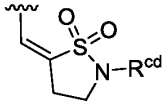


Formula II-A.

3. The compound is represented by:



Formula II-B.

4. A is selected from the group consisting of cyano, $–C(O)R^D$, $–C(O)CH_2N(R^bR^c)$, $–C(O)CH_2OC(O)R^D$, $–C(O)C(O)R^D$, $–(CH=CH)C(O)OR^D$, $–(CH=CCN)C(O)OR^D$, $–(CH=CCN)C(O)(NH)R^D$, $–CH(CN)(OH)$, $-CH(CN)(NR^bR^c)$,  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} – $N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

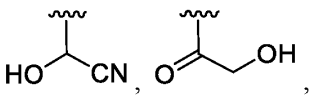
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

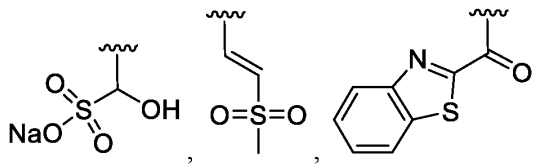
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -$N(R^bR^c)$, wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

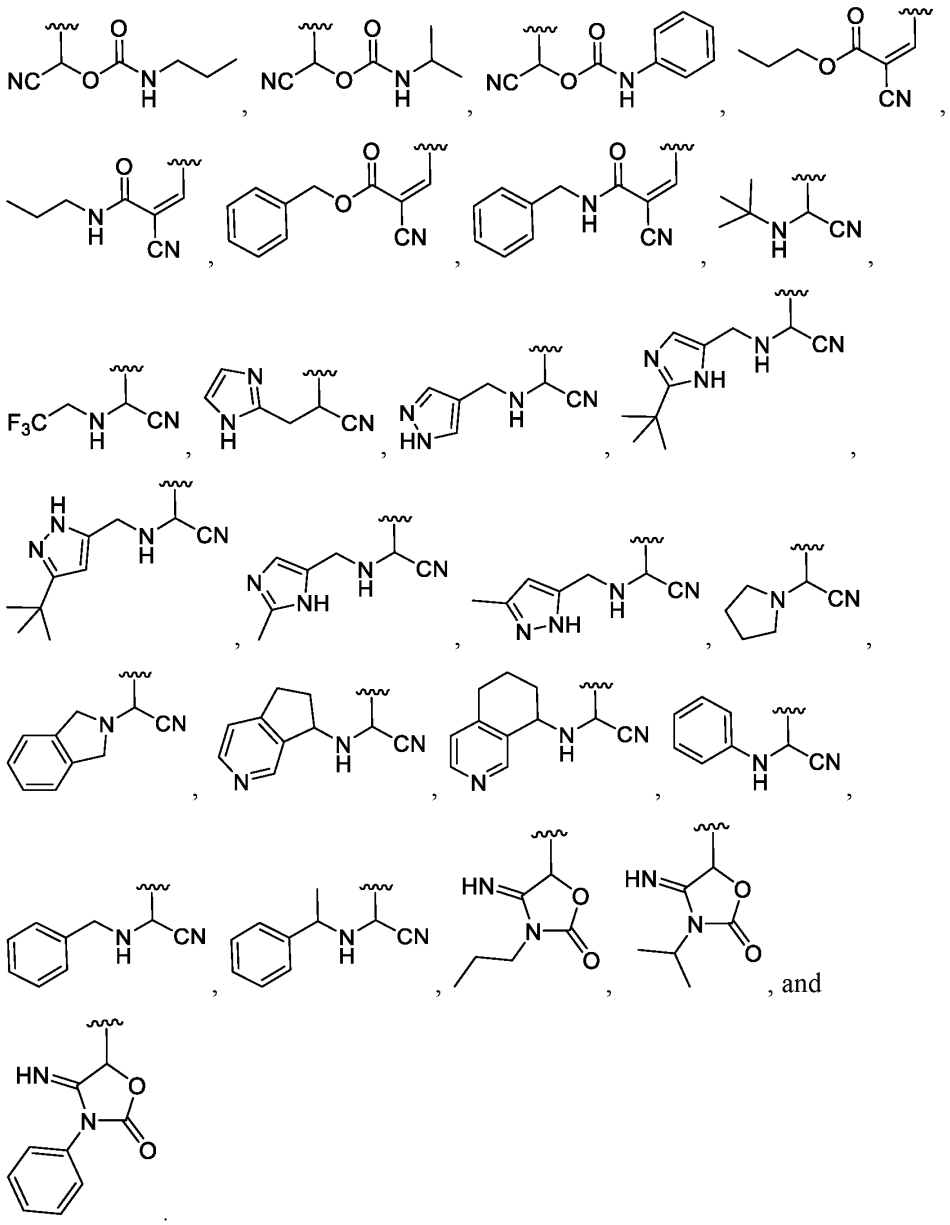
R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

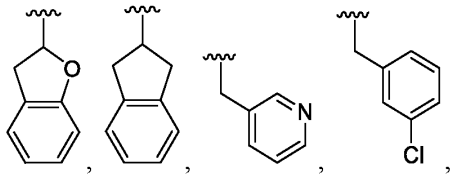
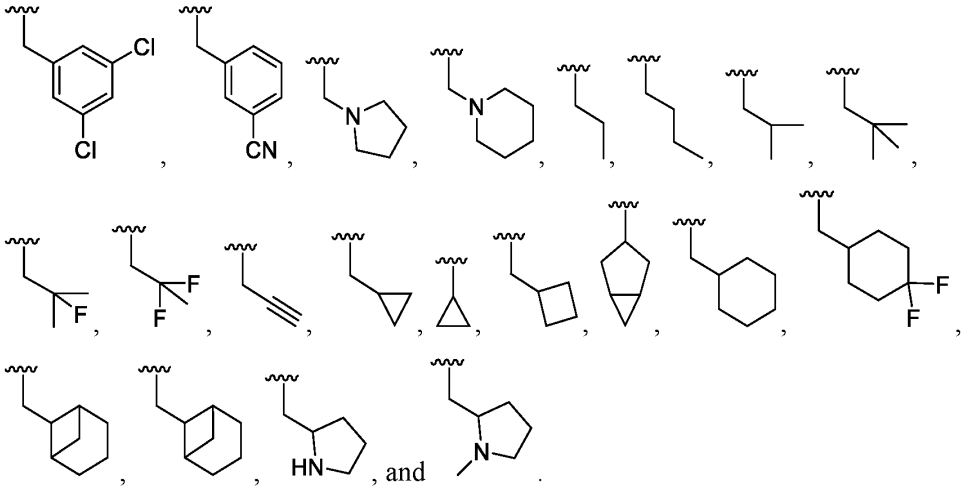
R^b and R^c are each selected from the group consisting of hydrogen, – $CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

5. A is selected from the group consisting of -CN, 

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6. R^{1a} is selected from the group consisting of  ,  , and .

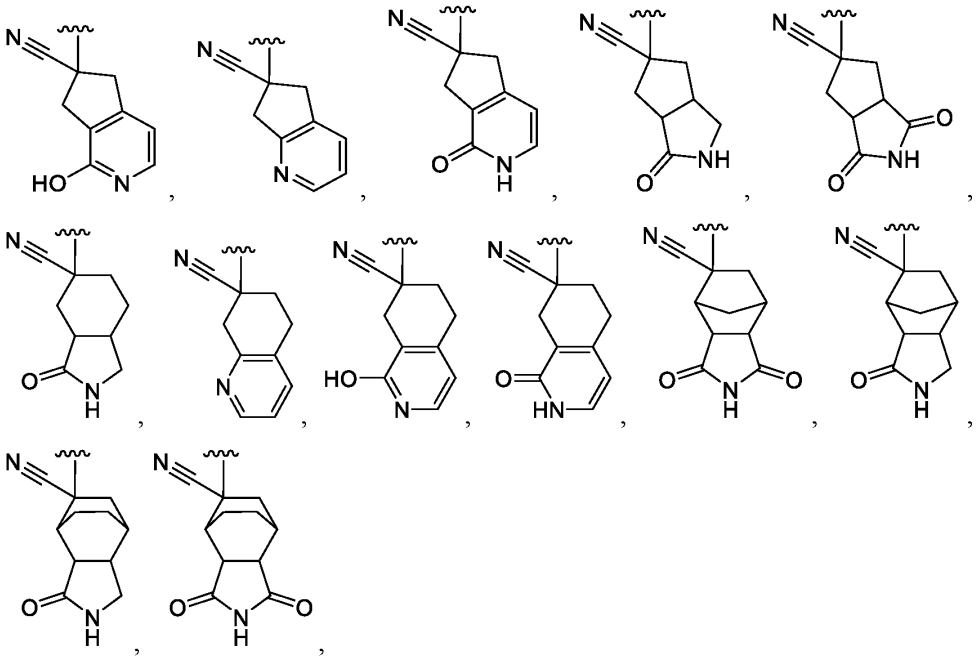
7. R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

8. R^{1b} is hydrogen.

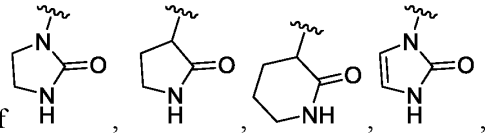
9. R^{1a} and R^{1b} are joined to together to form  .

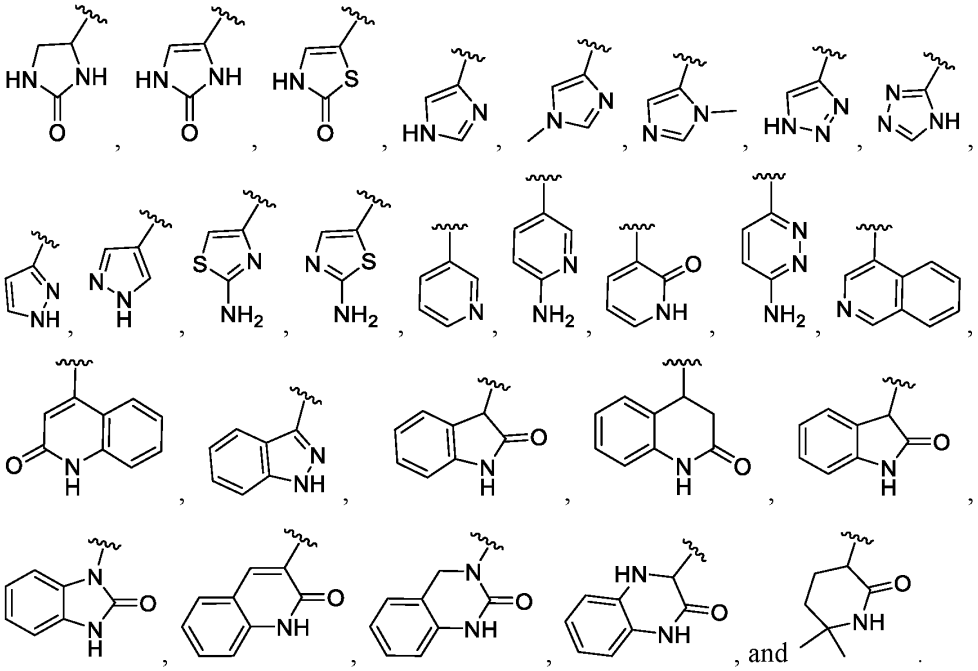
10. R^{3a} is a 4-10 membered heterocycle substituted by A.

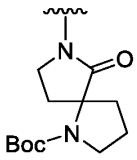
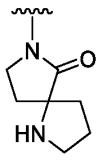
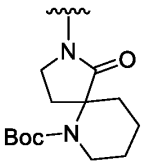
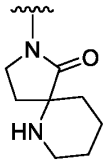
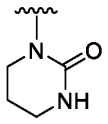
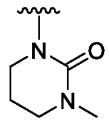
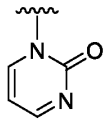
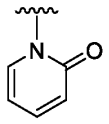
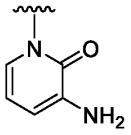
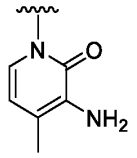
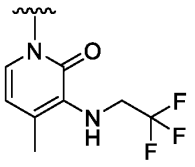
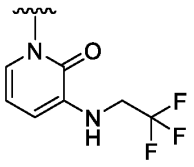
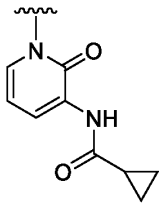
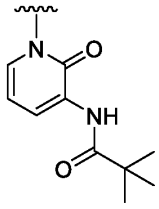
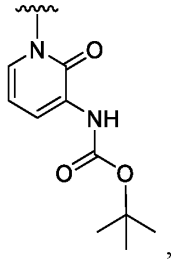
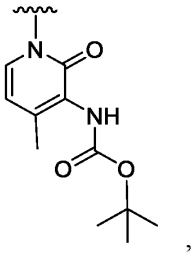
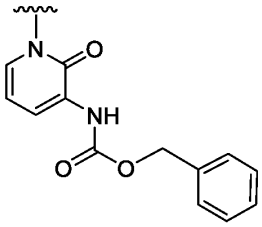
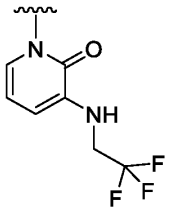
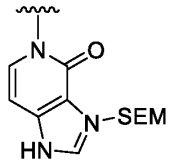
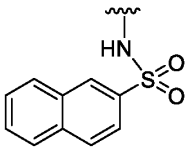
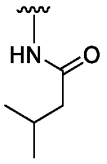
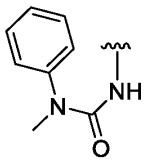
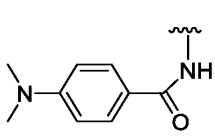
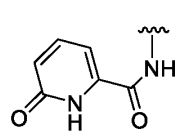
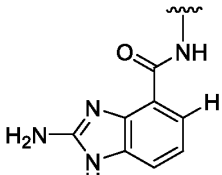
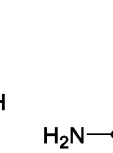
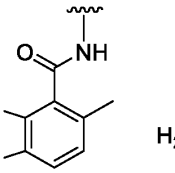
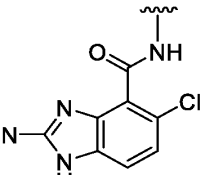
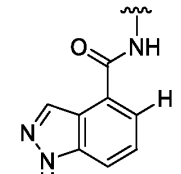
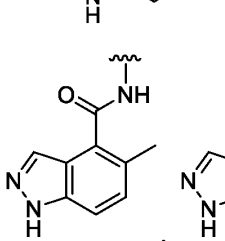
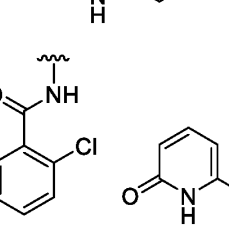
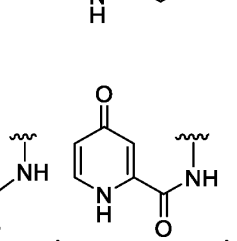
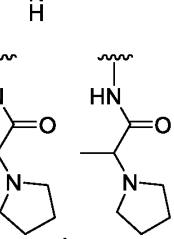
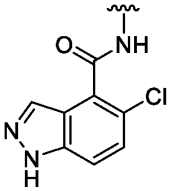
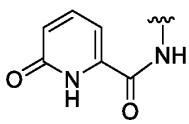
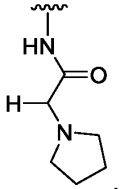
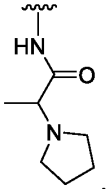
11. R^{3a} is selected from the group consisting of

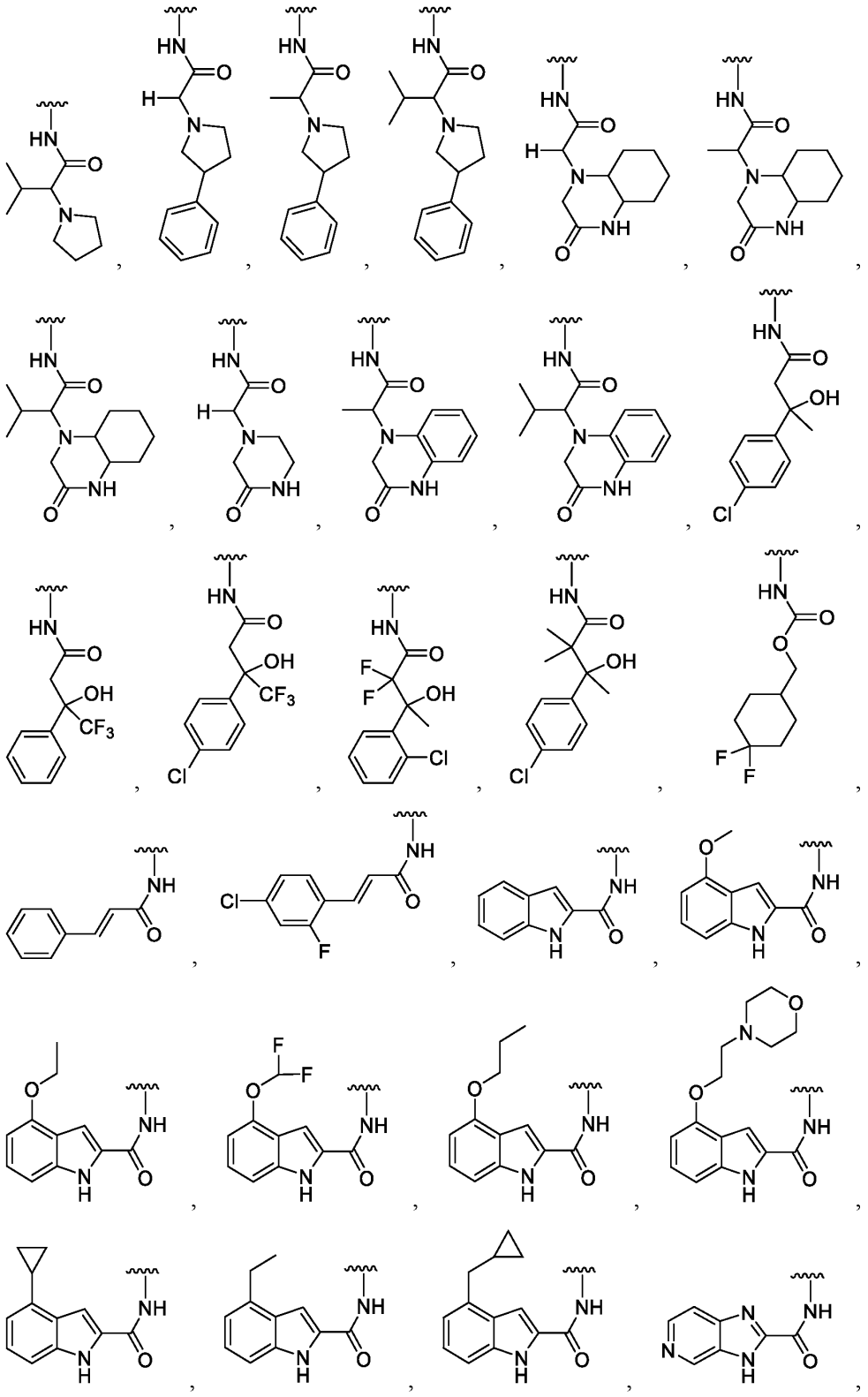


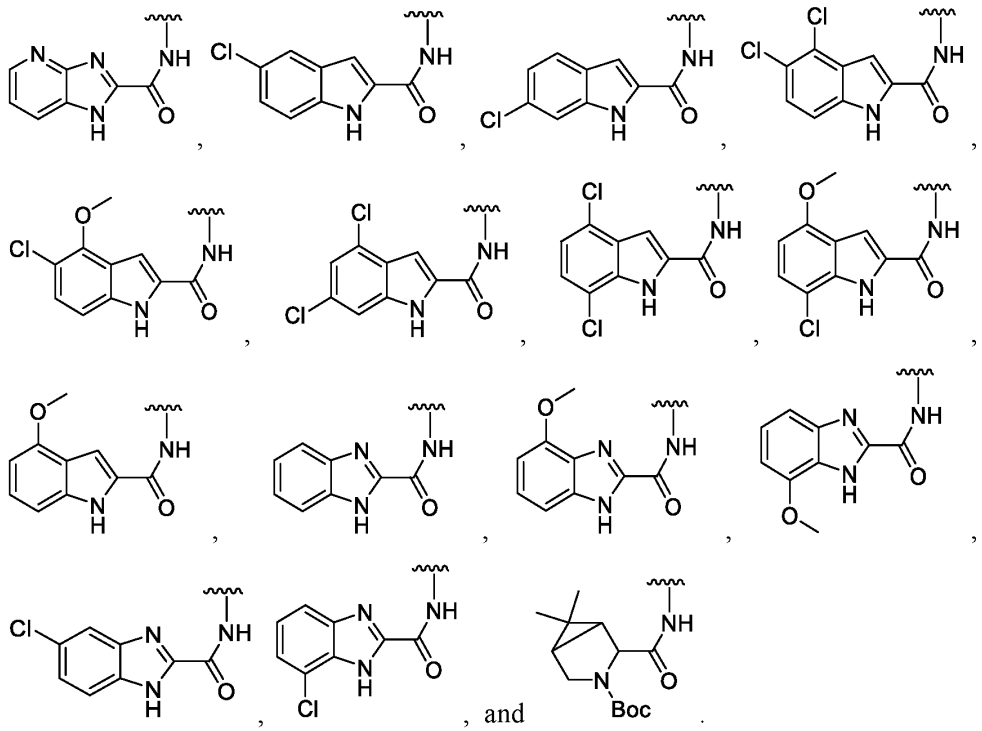
12. R^3 is a 4-10 membered heterocycle.

13. R^3 is selected from the group consisting of 

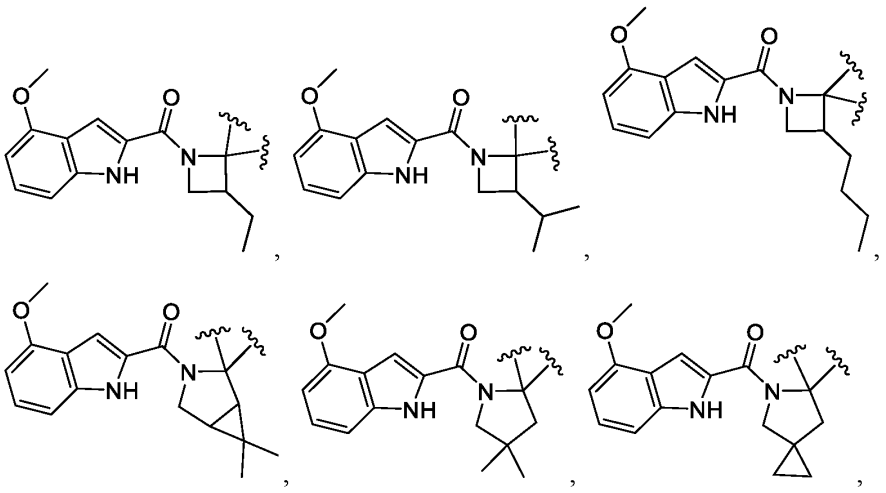


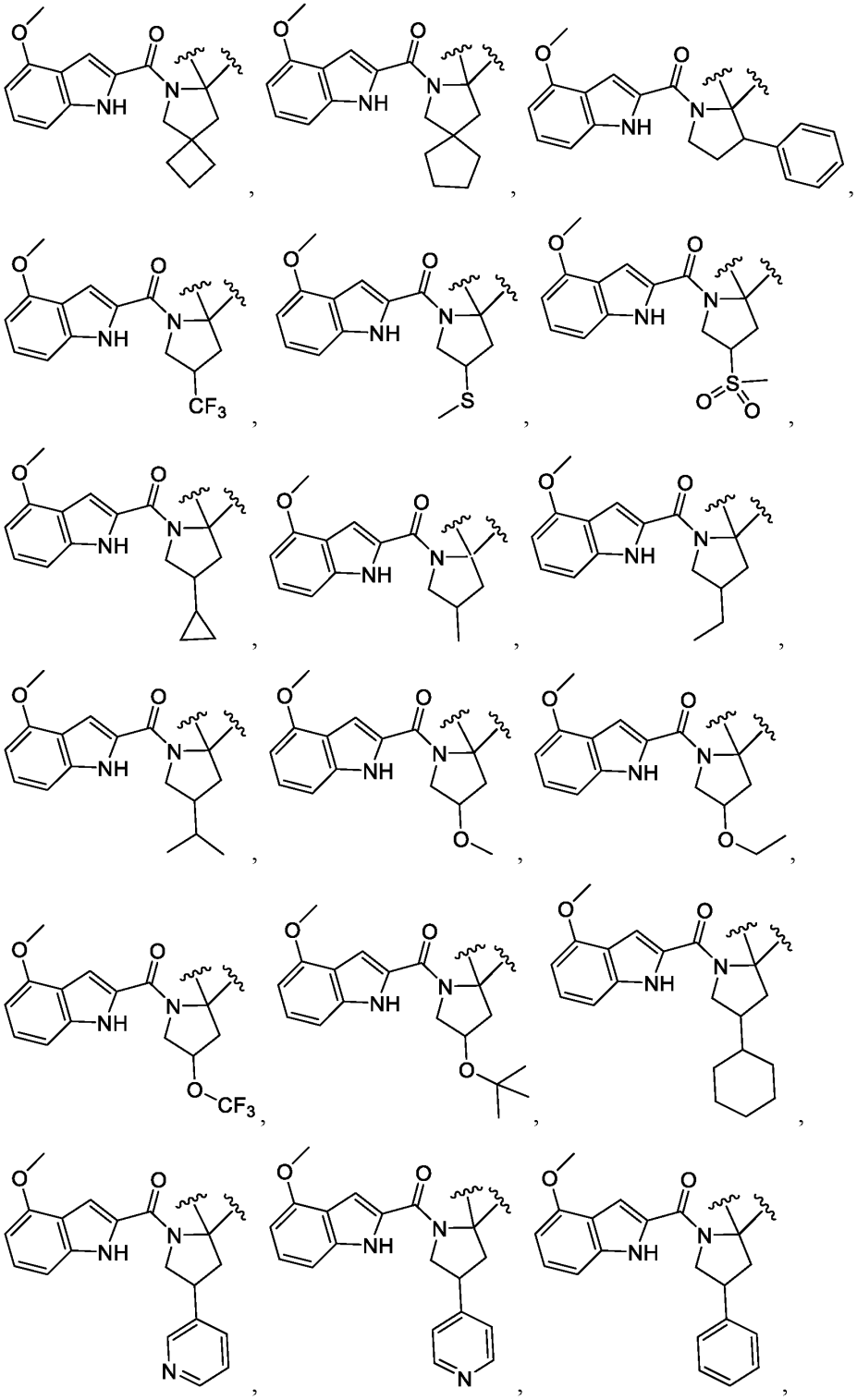
14. R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  , ,  ,  .

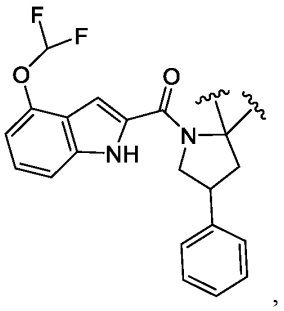
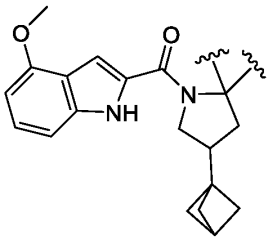
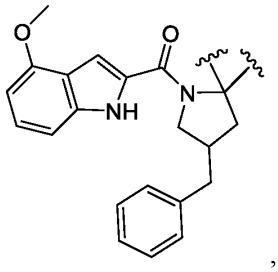
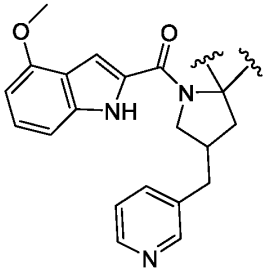
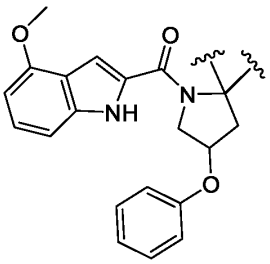
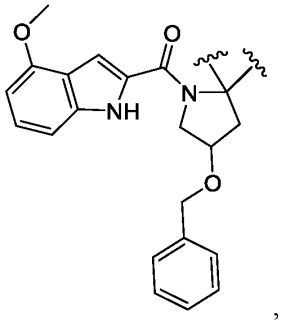
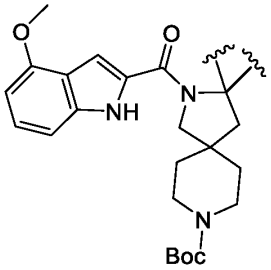
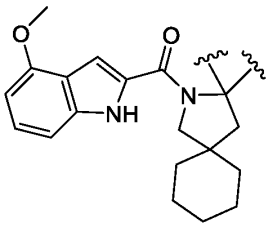
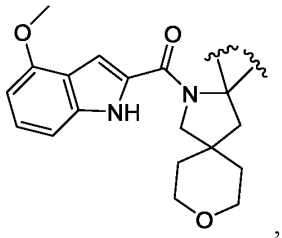
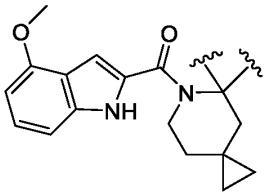
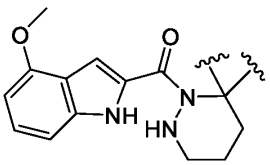
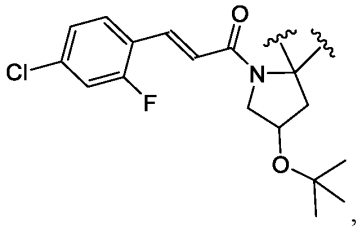
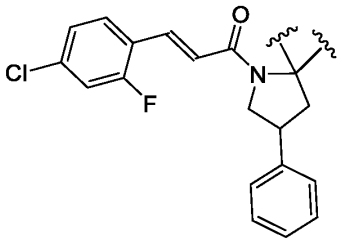




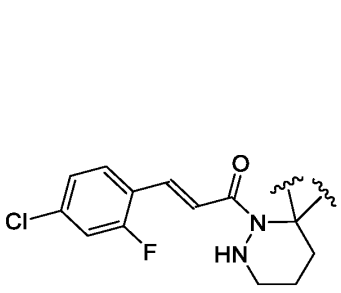
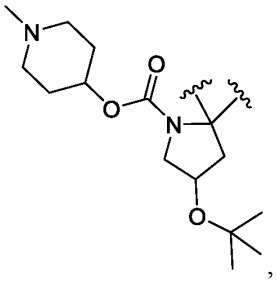
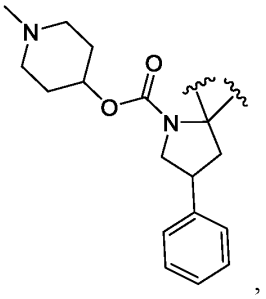
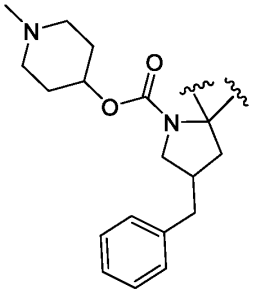
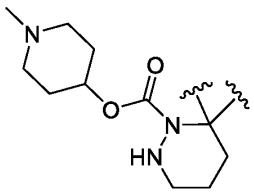
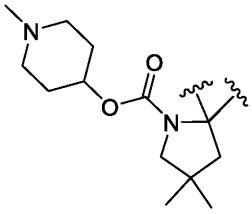
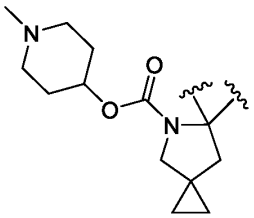
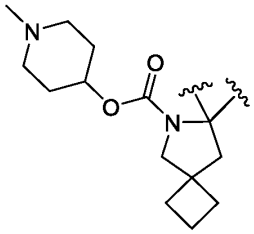
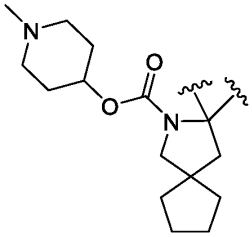
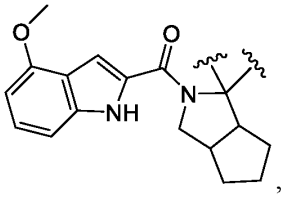
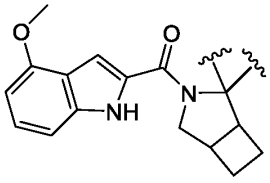
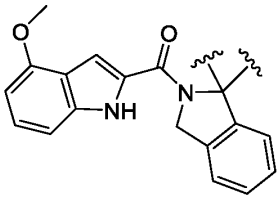
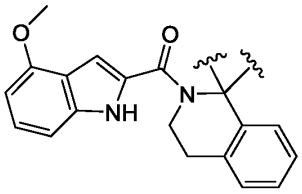
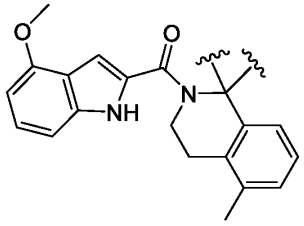
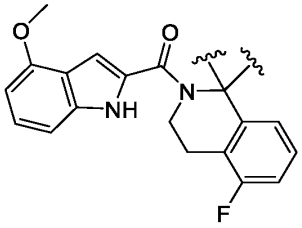
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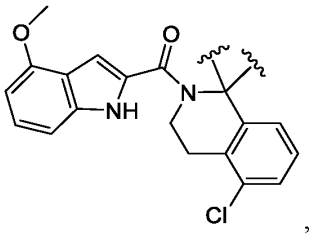
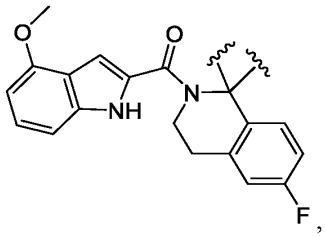
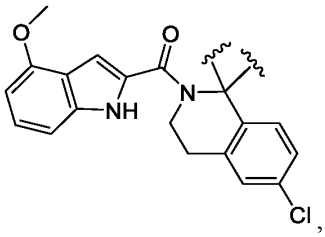
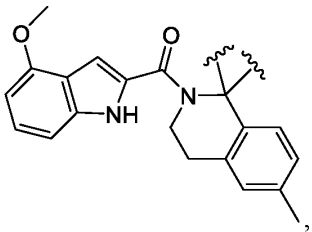
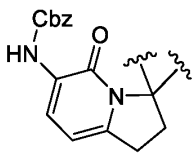
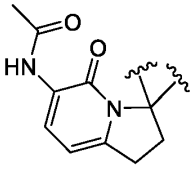
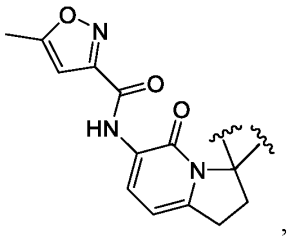
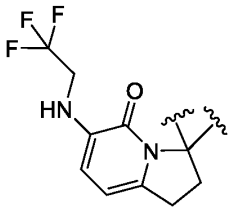
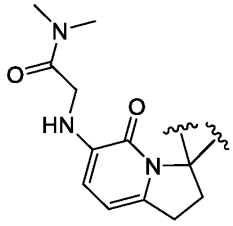
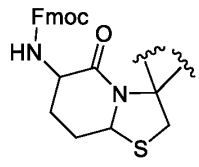
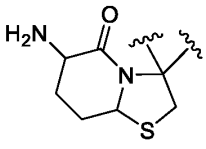
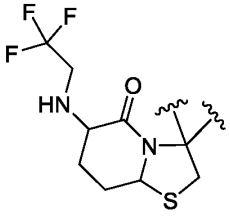
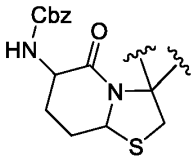
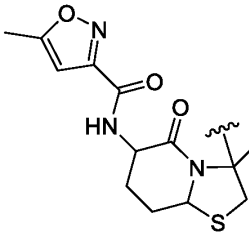
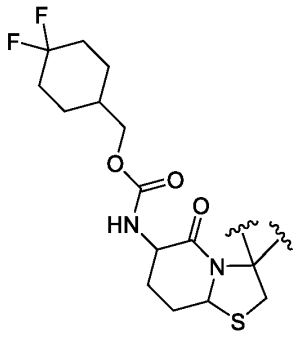


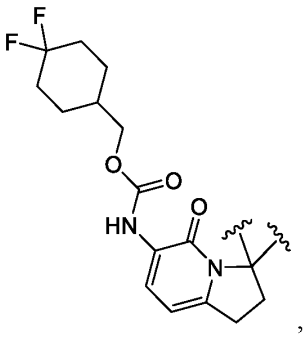
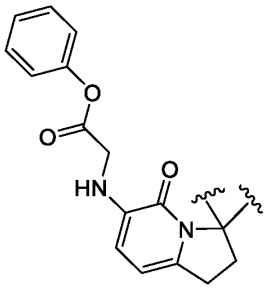
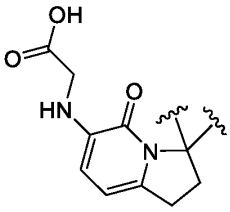
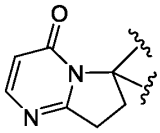



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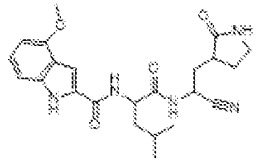
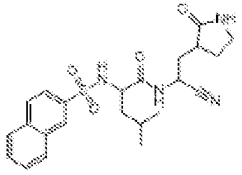
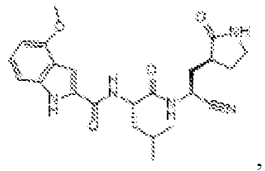
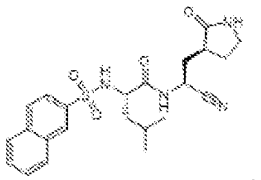
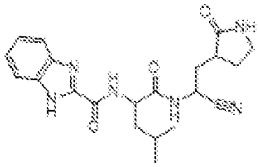
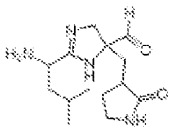
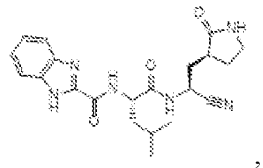
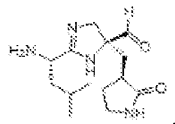
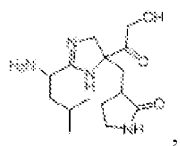
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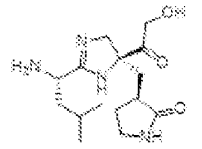
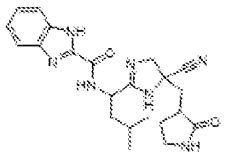
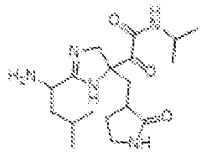
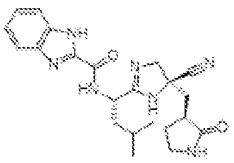
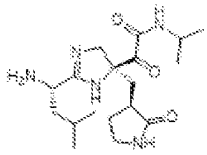
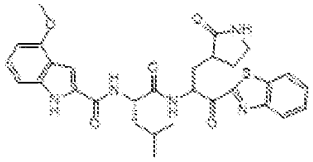
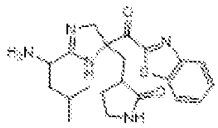
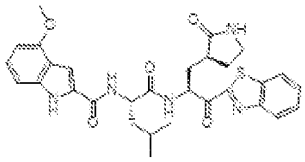
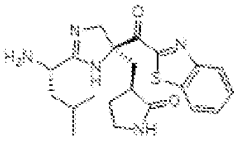
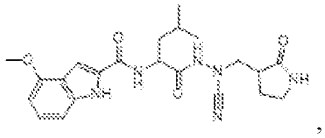
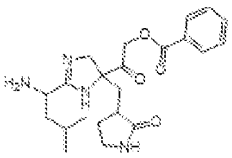
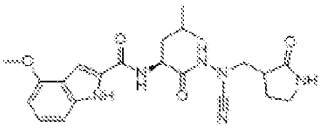
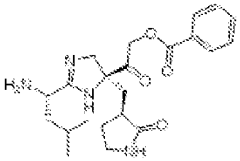
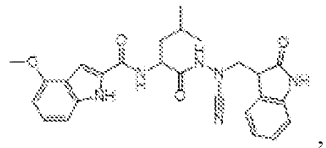
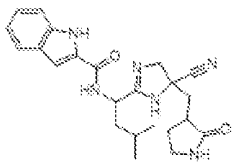
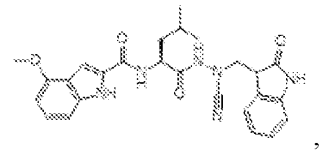
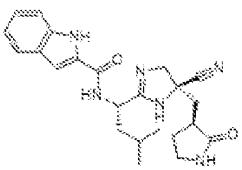
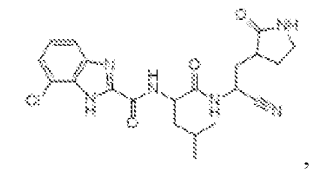

















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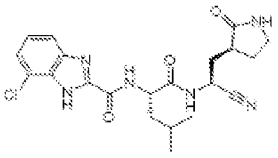
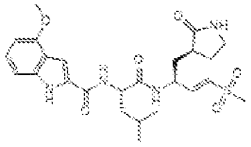
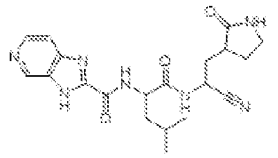
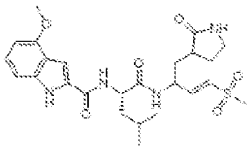
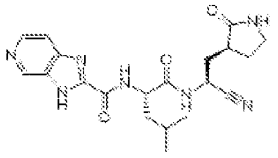
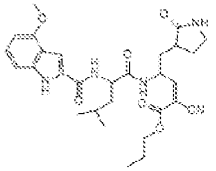
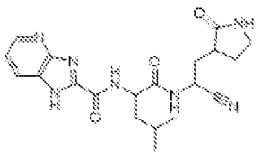
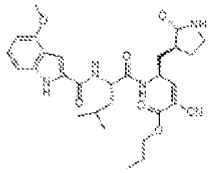
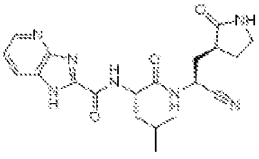
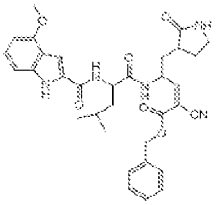
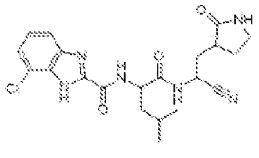
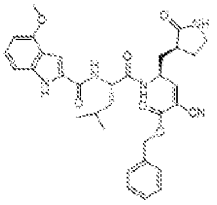
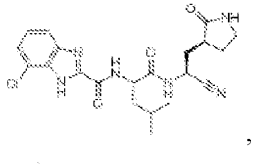
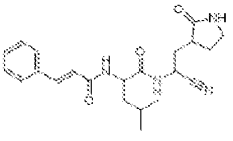
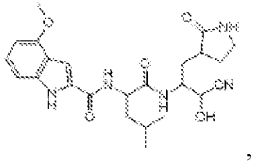
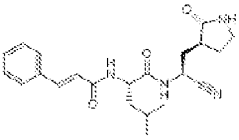
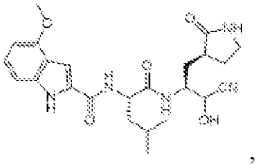
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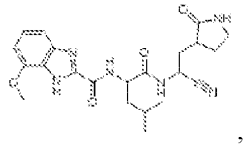

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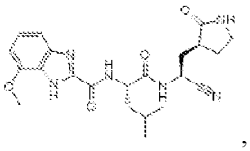

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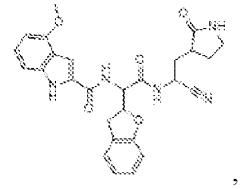
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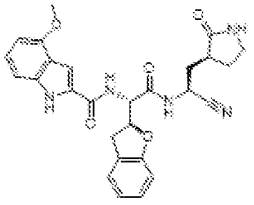
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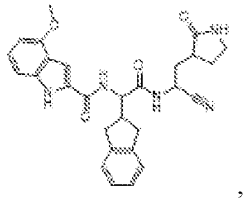

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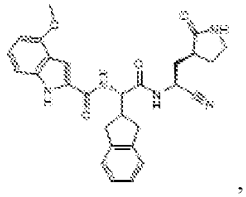

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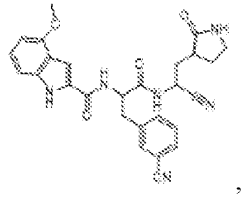

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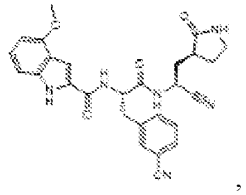

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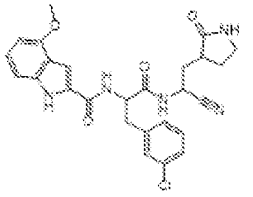

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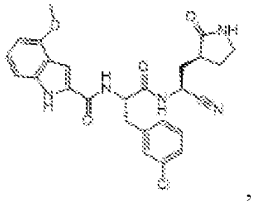

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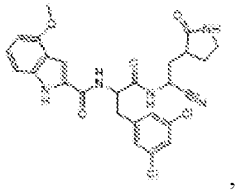

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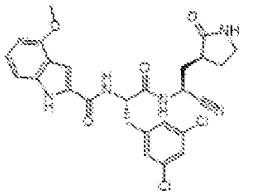

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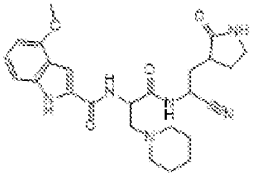

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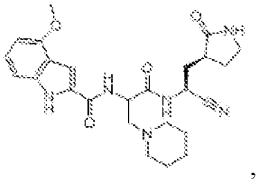

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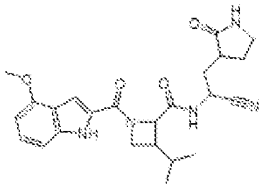

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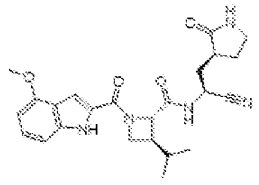
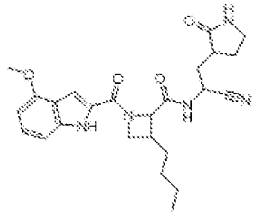
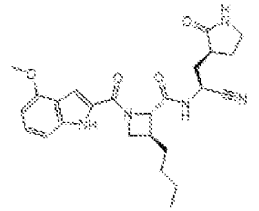
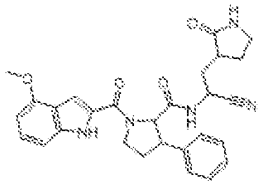
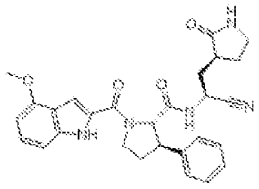
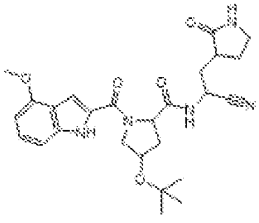
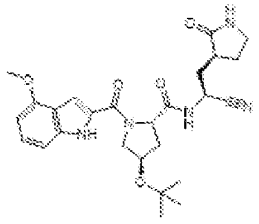
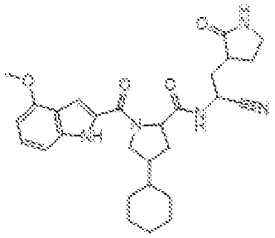
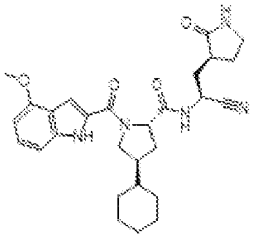
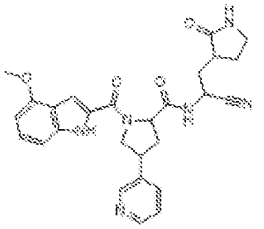
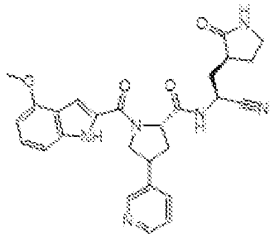
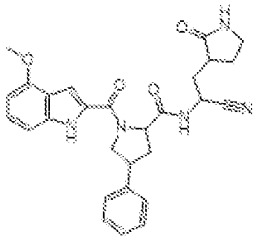
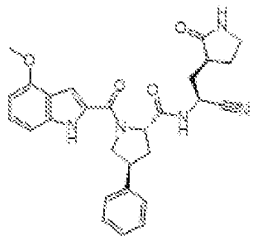

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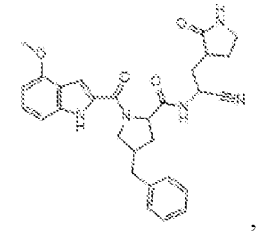

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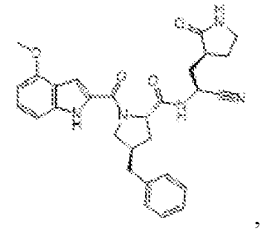

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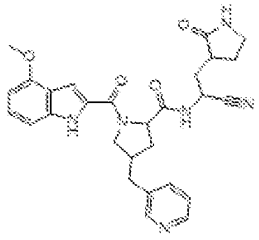

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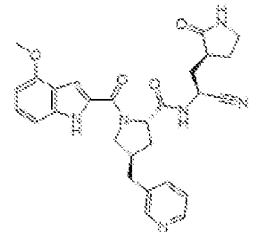
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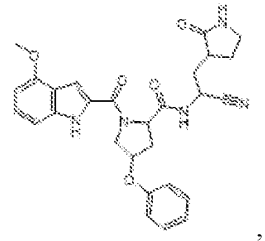
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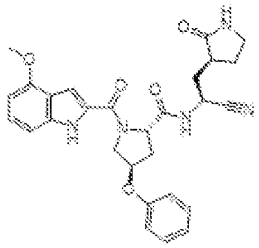
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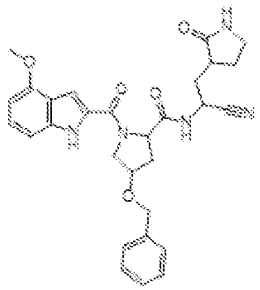
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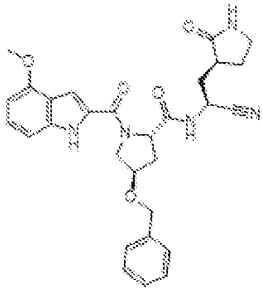
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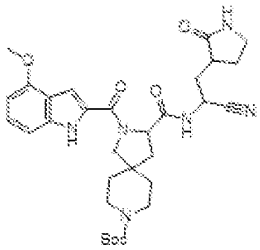
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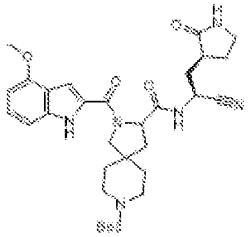
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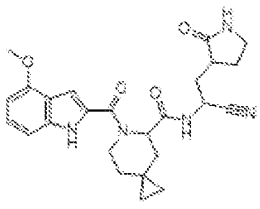
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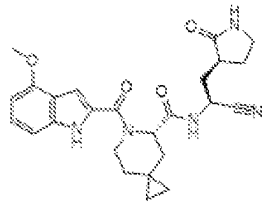
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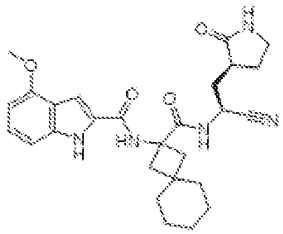
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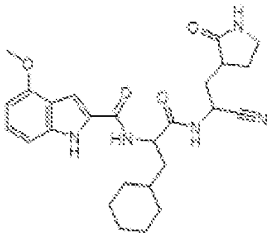
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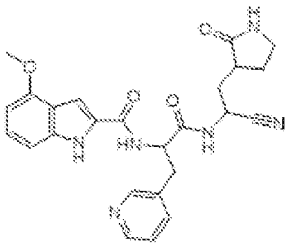
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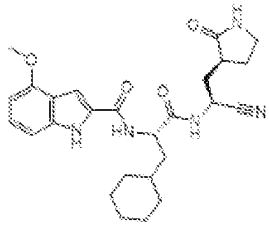
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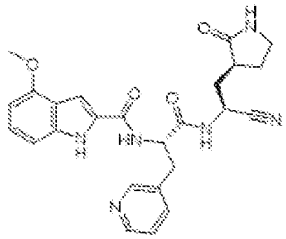
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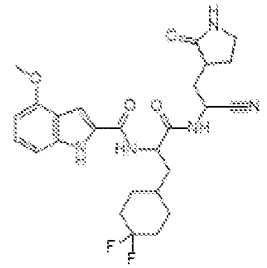
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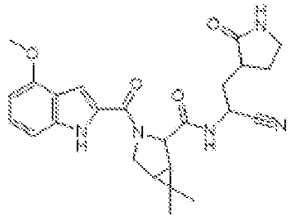
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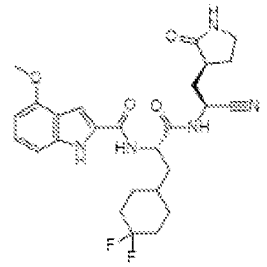
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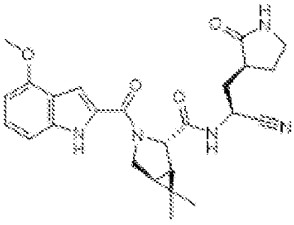
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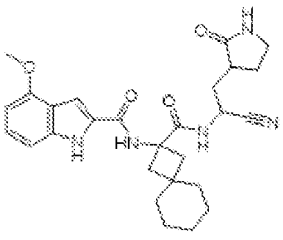
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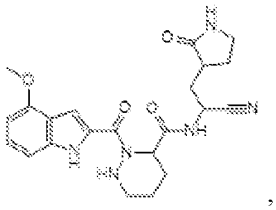
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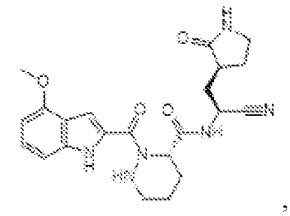
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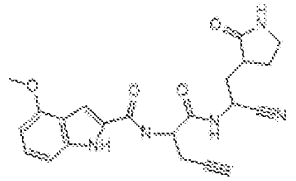
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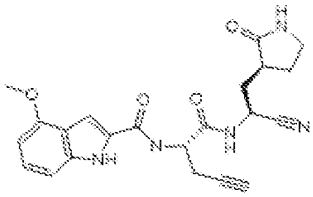
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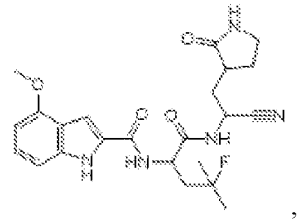
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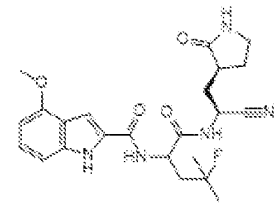
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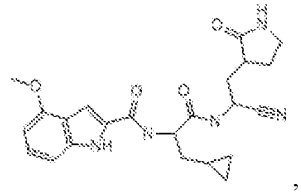
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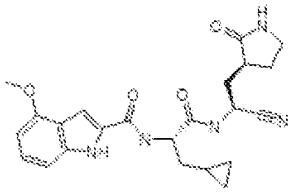
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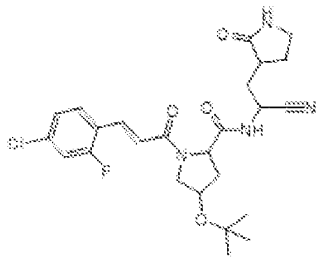
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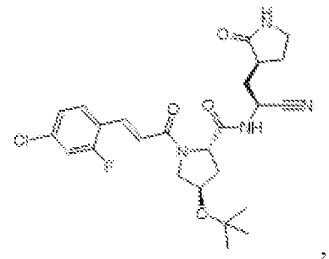
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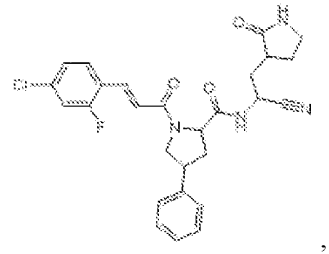
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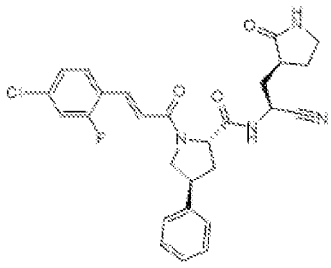
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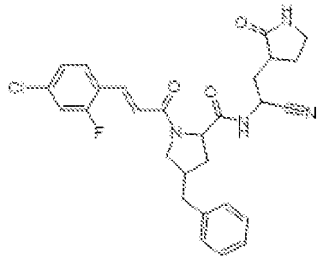
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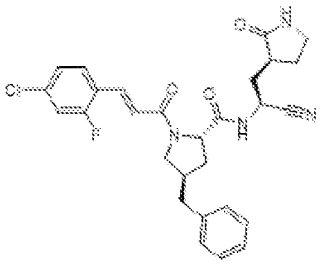
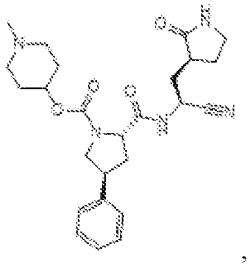
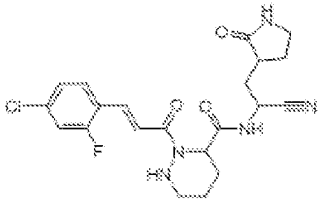
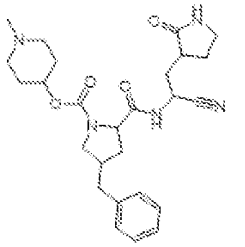
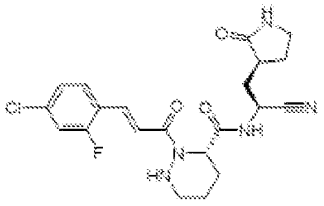
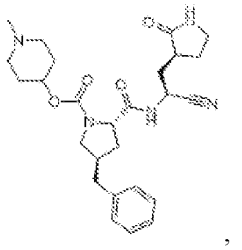
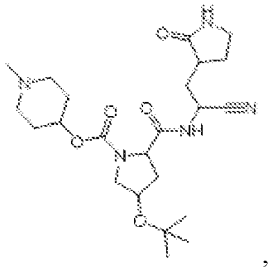
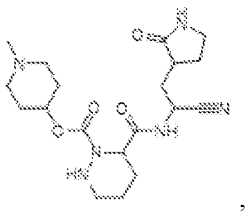
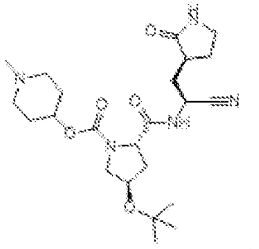
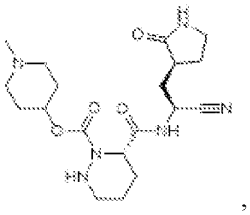
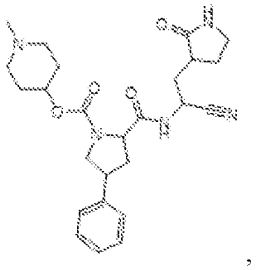
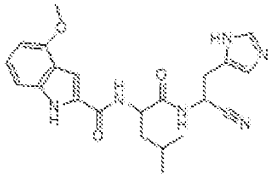
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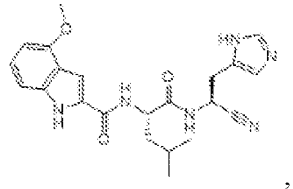
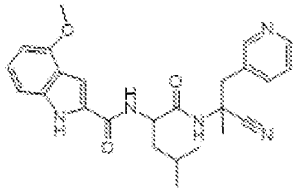
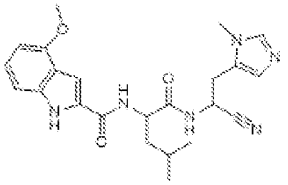
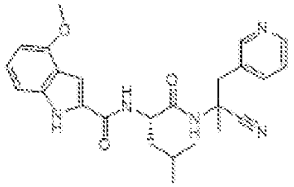
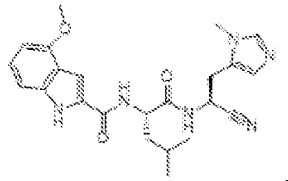
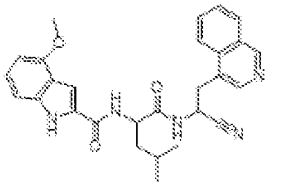
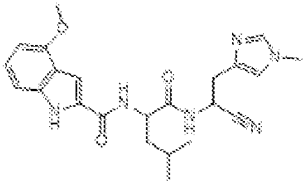
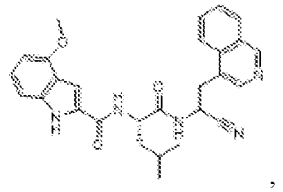
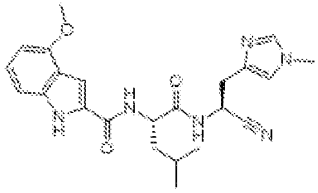
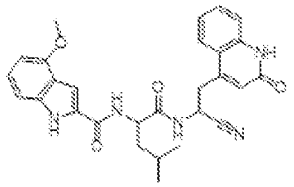
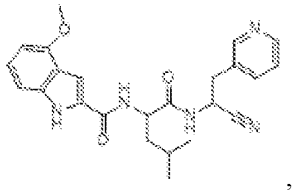
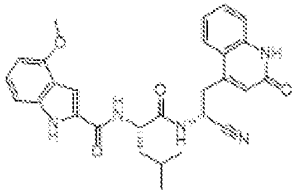
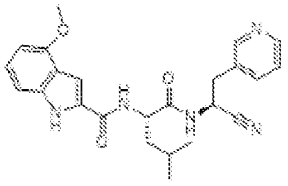
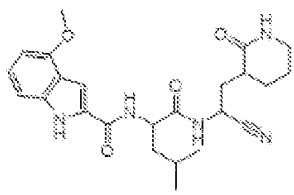


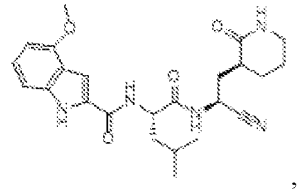
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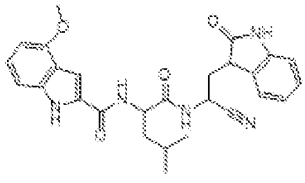
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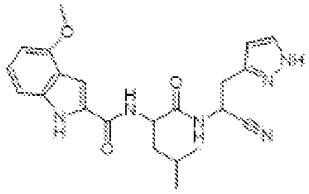

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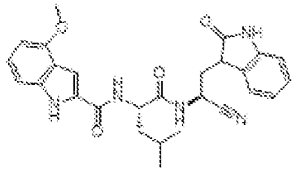
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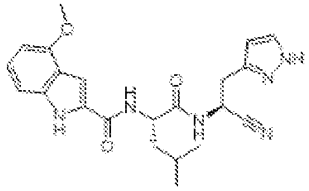
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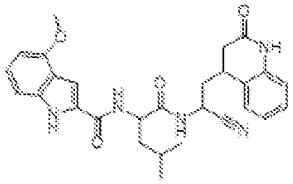
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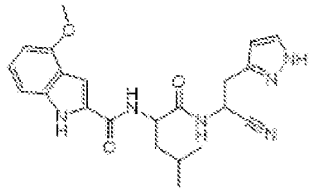
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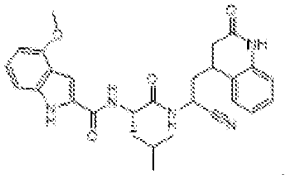
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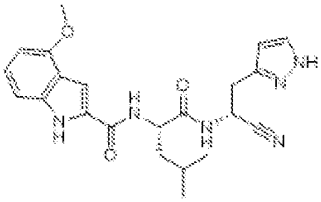
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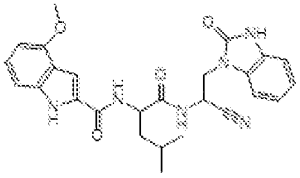
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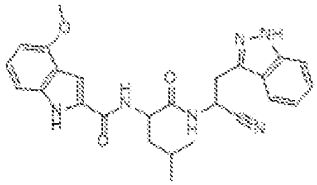
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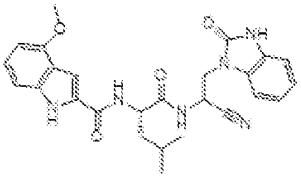
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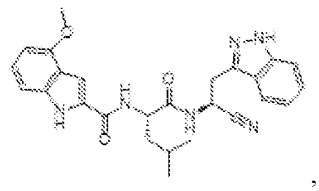
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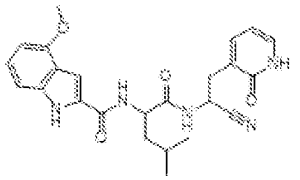
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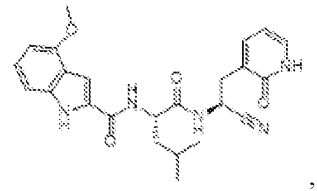
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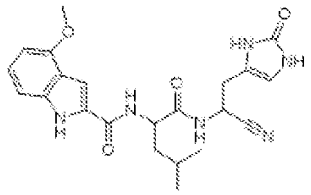
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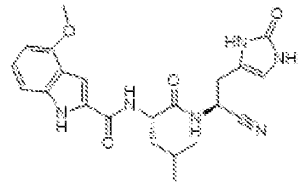
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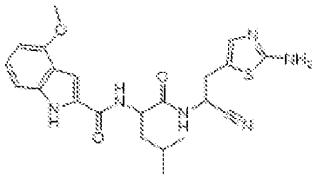
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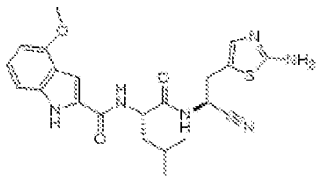
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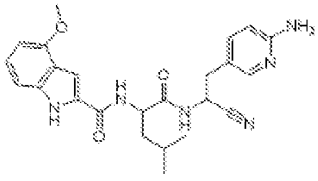
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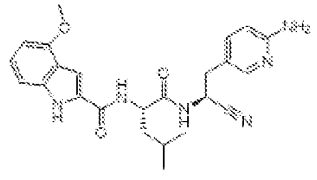
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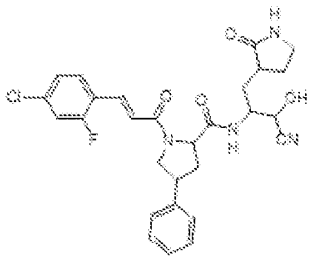
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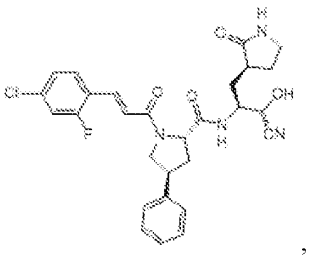
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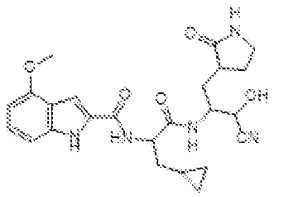
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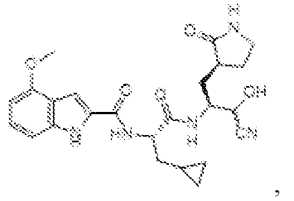
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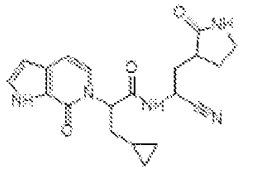
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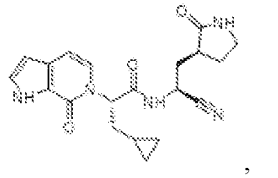
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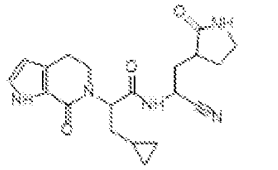
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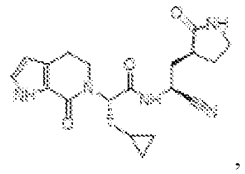
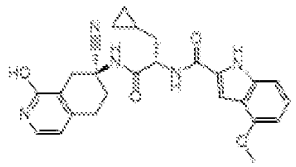
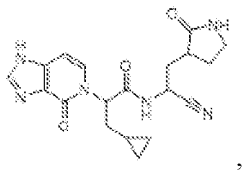
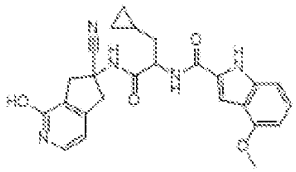
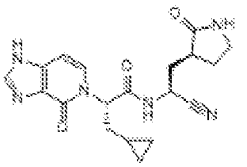
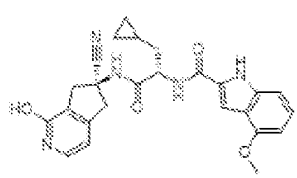
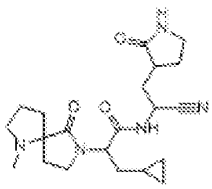
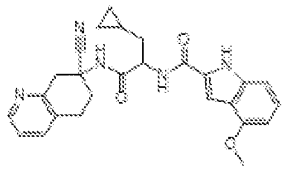
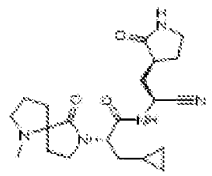
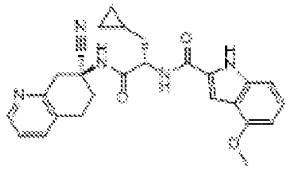
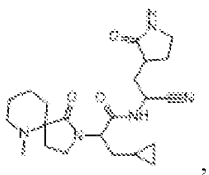
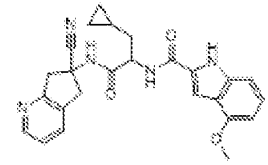
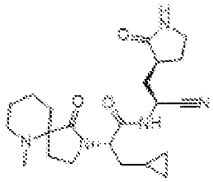
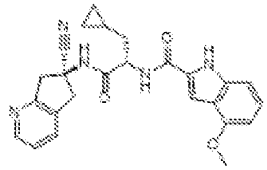
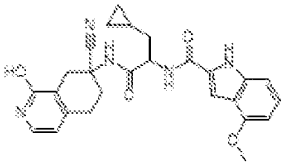
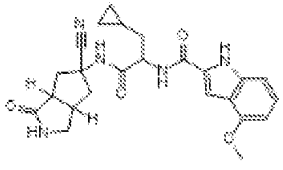
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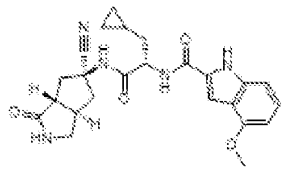


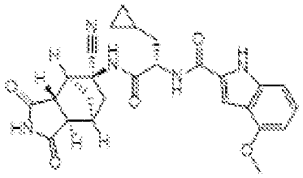
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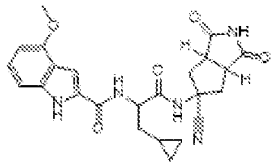


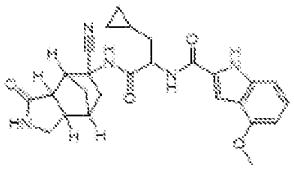
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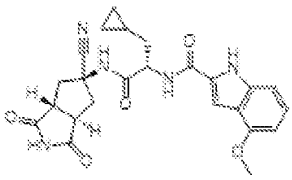

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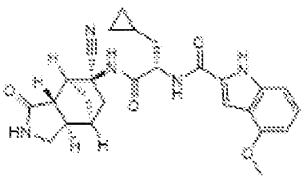
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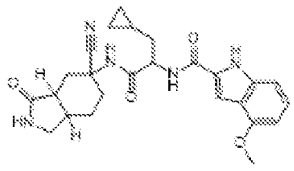
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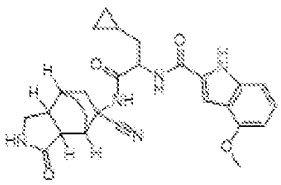
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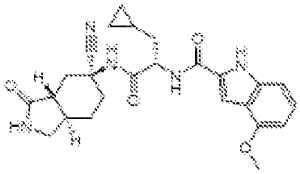
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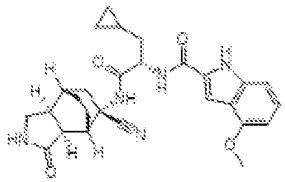
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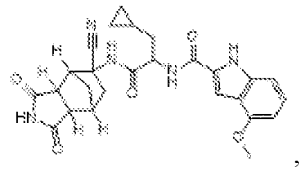
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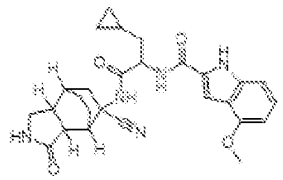
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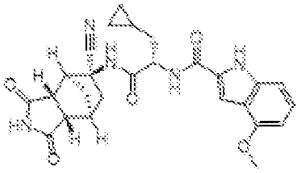
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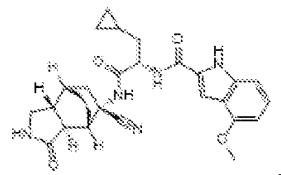
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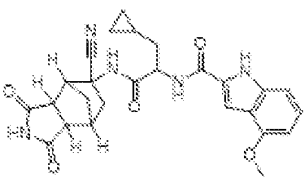
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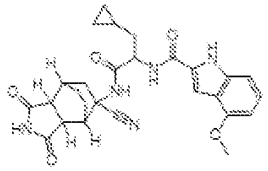
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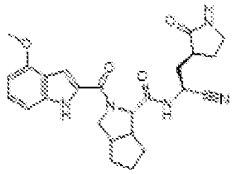
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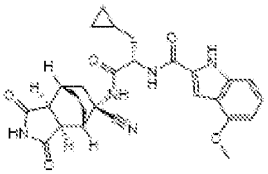
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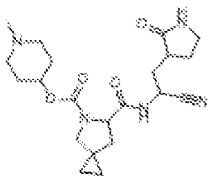
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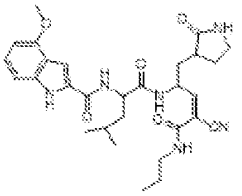
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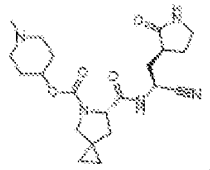
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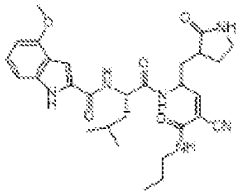
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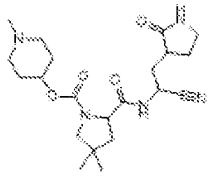
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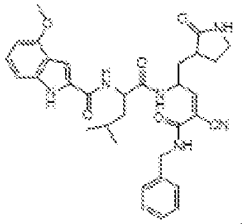
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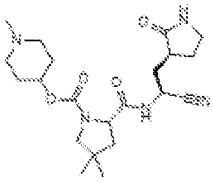
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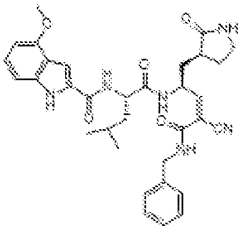
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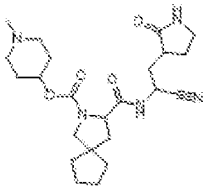
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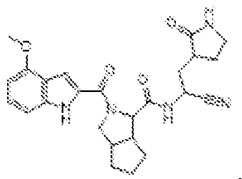
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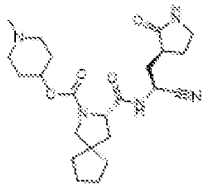
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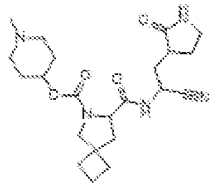
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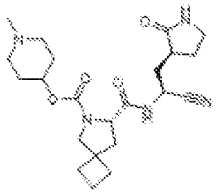
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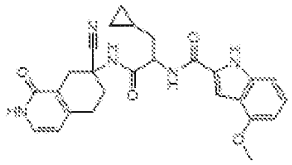
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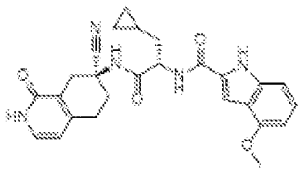
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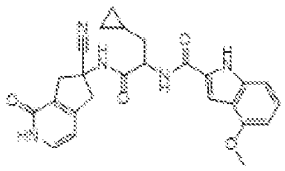
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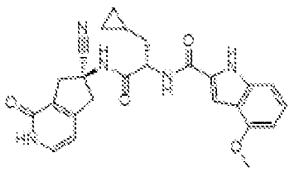
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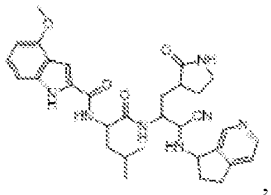
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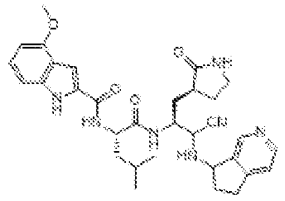
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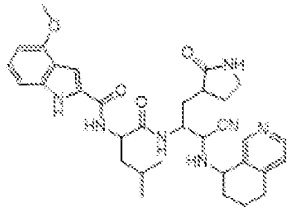
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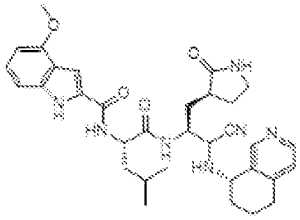
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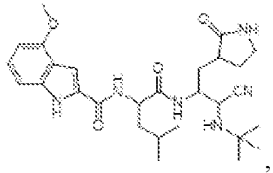
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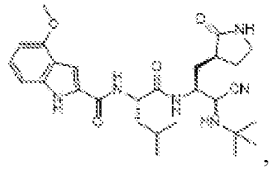
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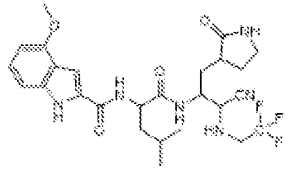
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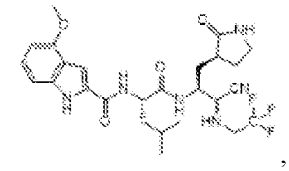
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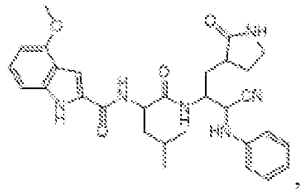
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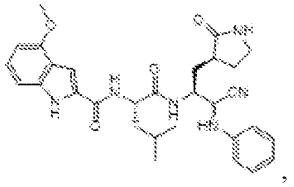


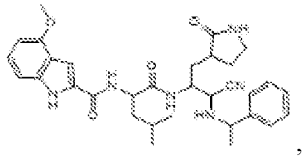
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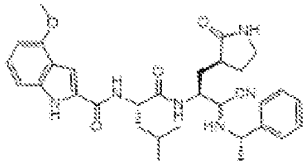


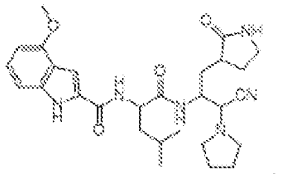
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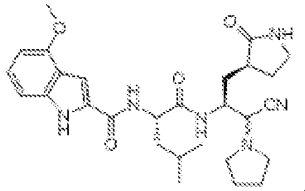
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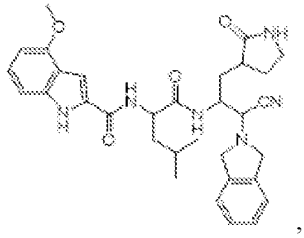
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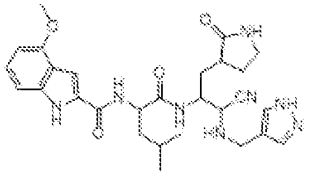
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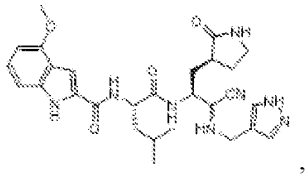
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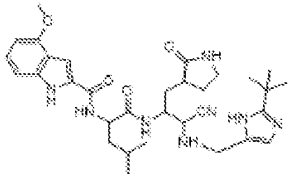
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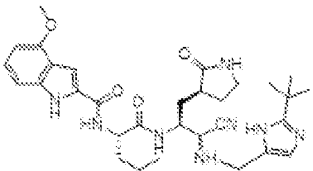
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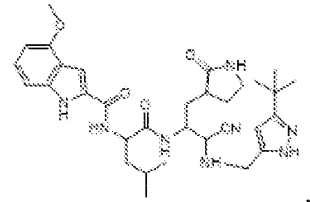
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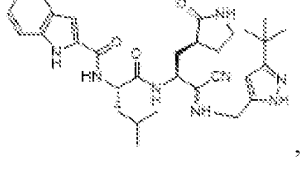
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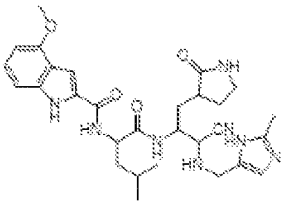
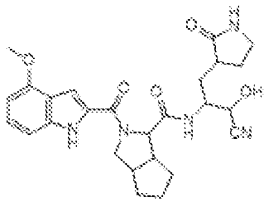
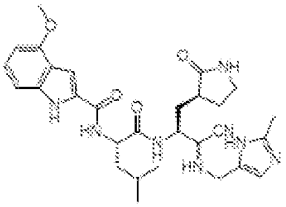
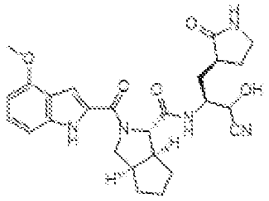
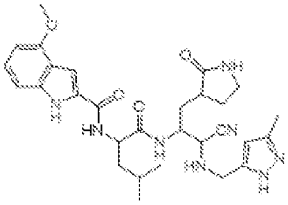
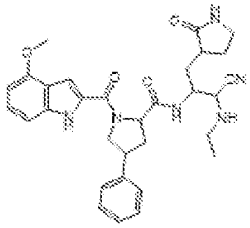
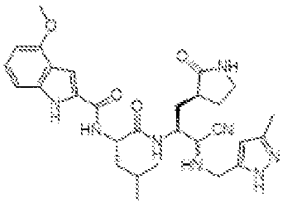
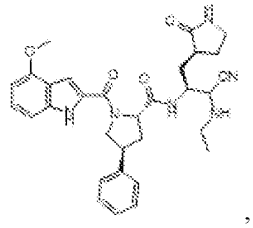
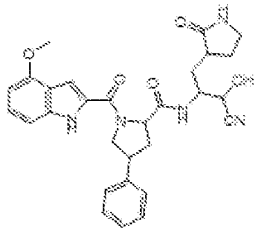
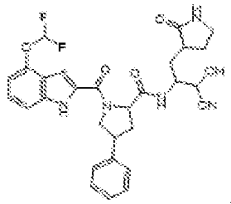
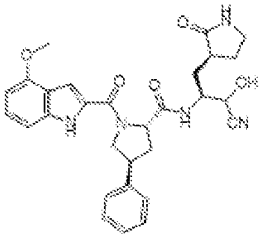
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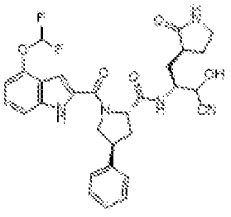
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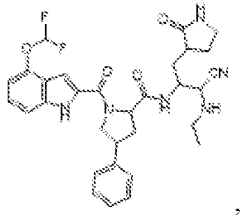
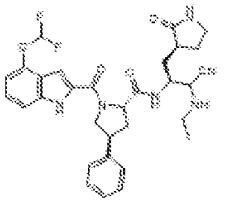
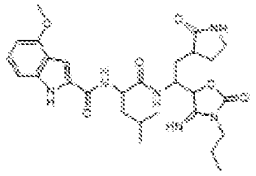
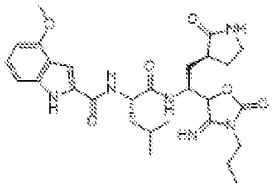
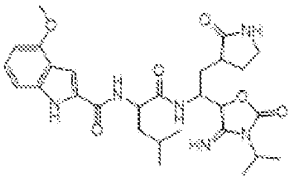
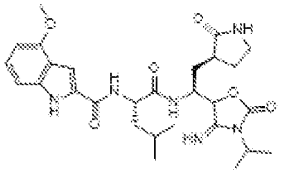
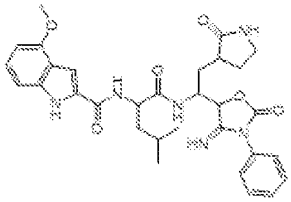
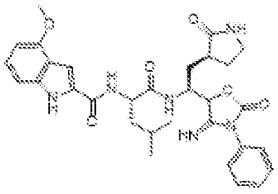
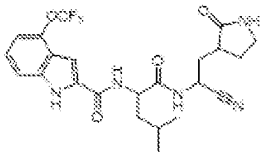
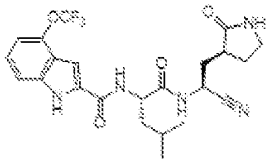
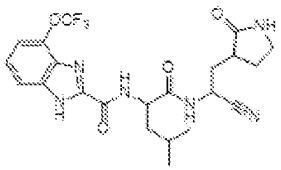
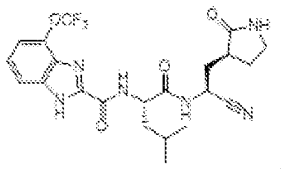
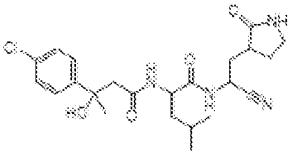
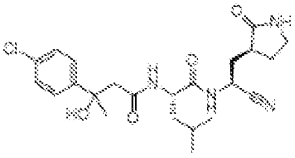
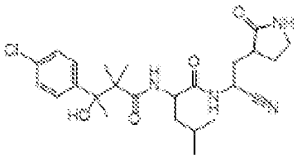
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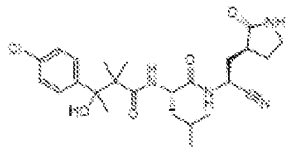
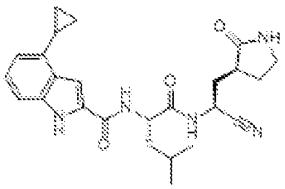
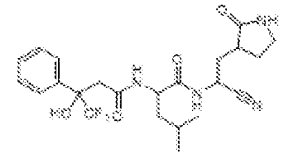
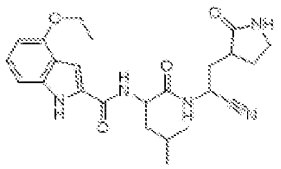
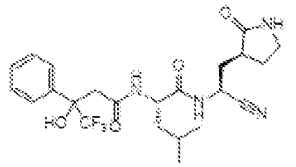
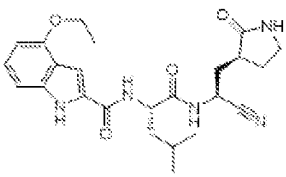
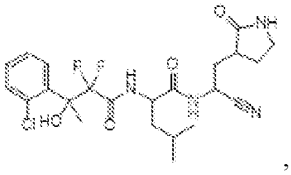
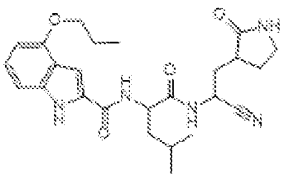
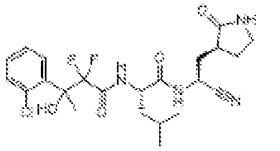
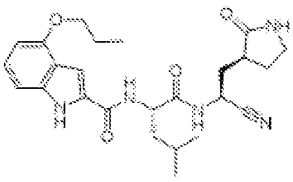
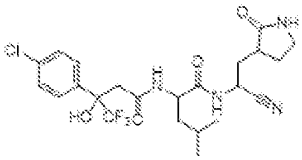
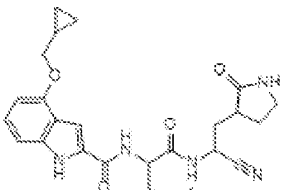
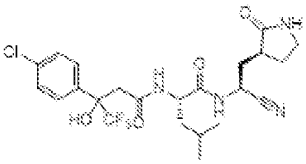
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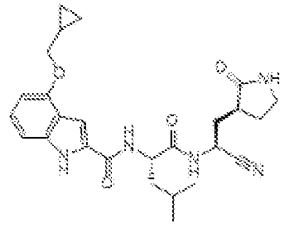
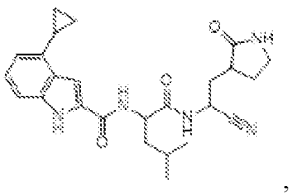
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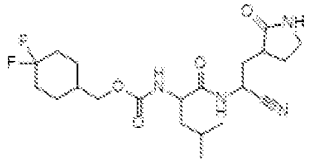

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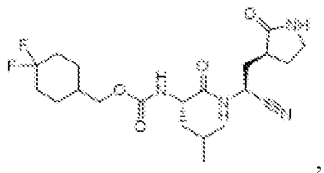
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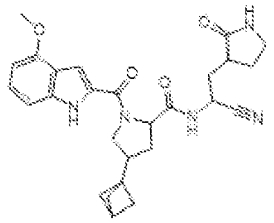
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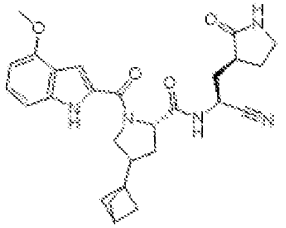
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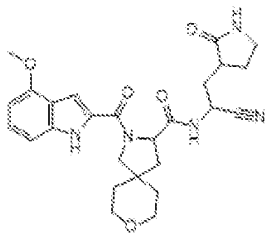
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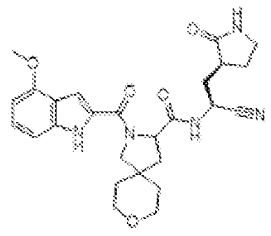
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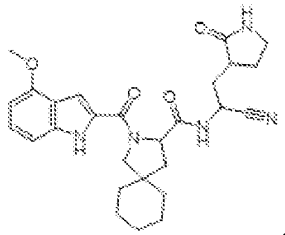
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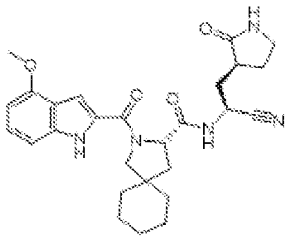
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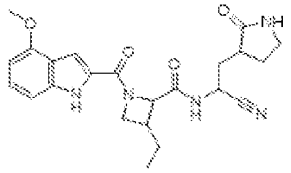
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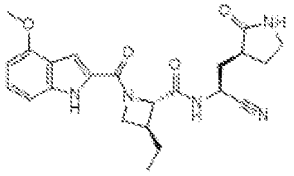
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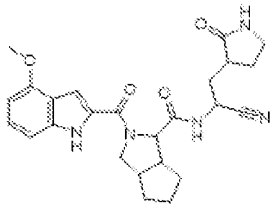
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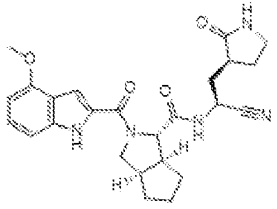
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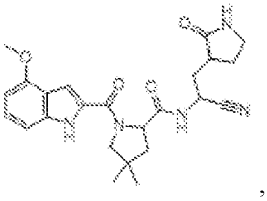
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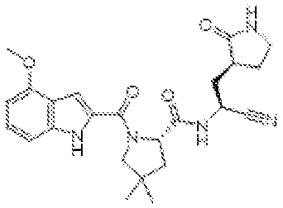
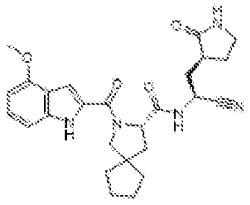
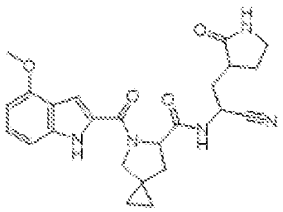
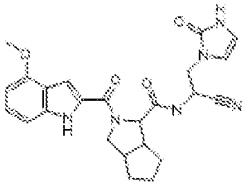
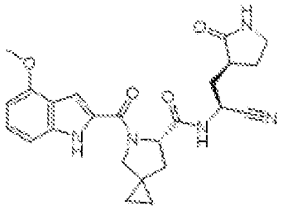
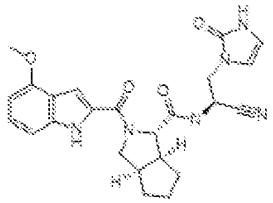
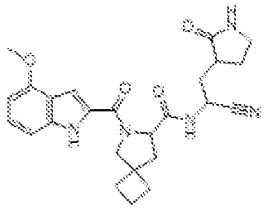
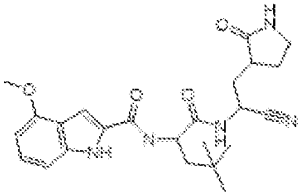
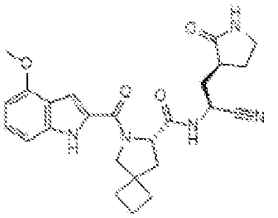
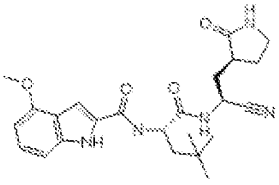
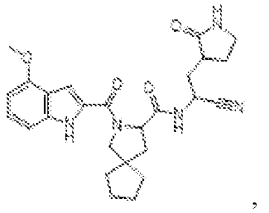
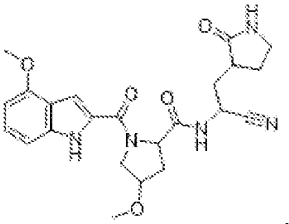
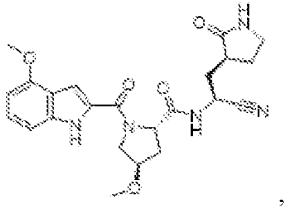


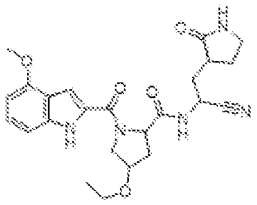
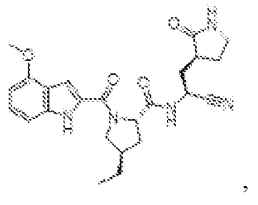
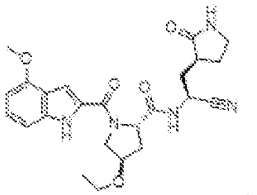
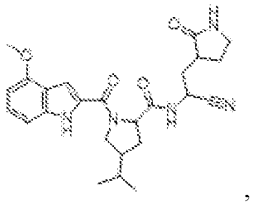
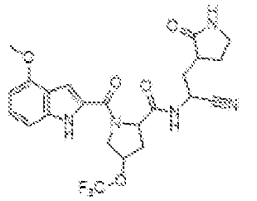
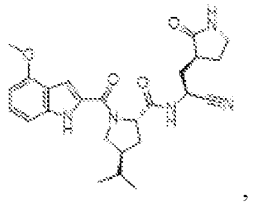
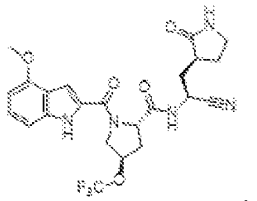
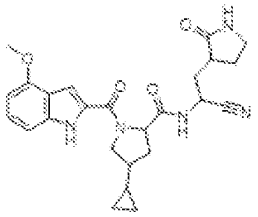
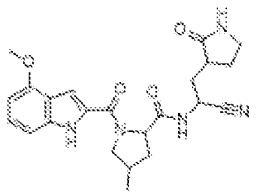
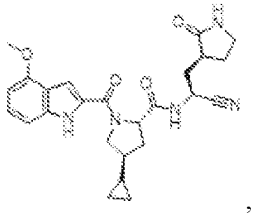
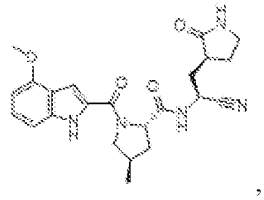
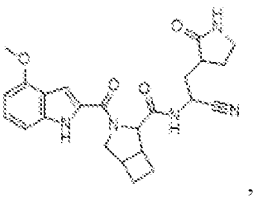
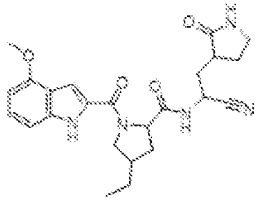
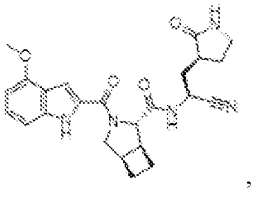
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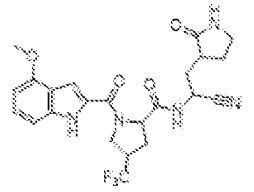


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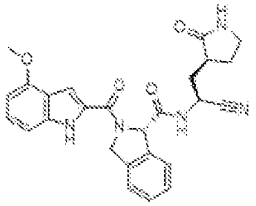



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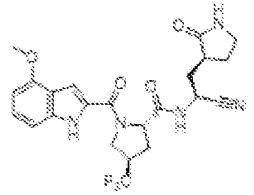

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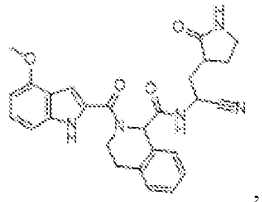
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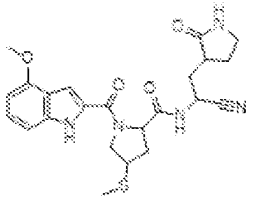
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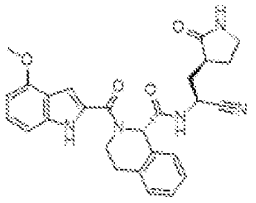
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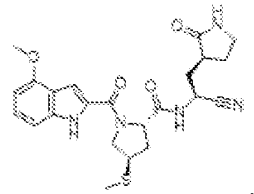
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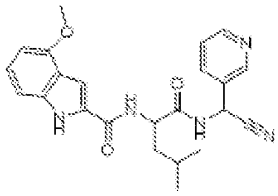
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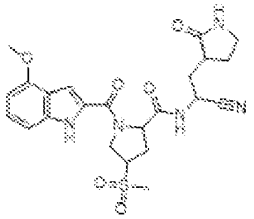
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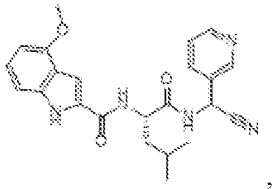
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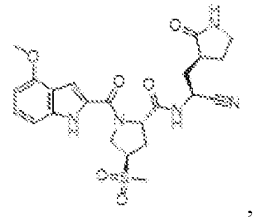
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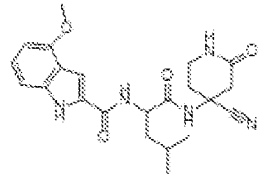
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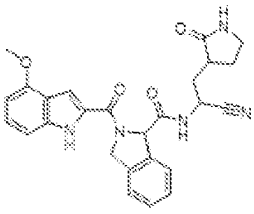
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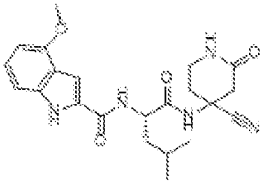
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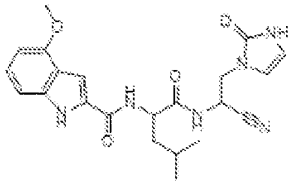


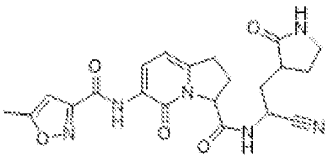
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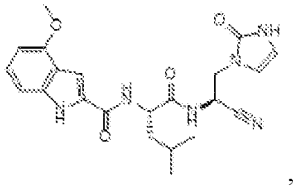


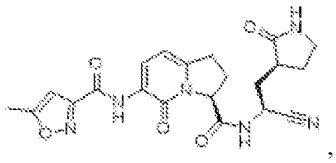
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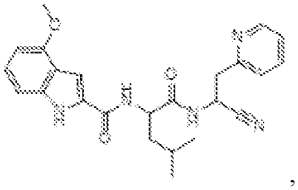
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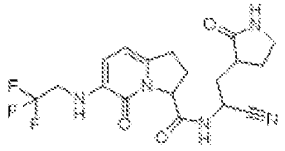

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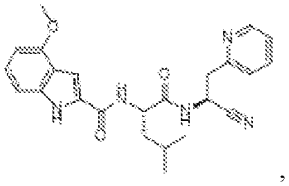

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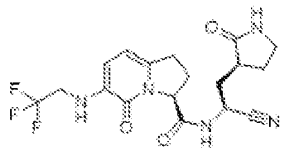

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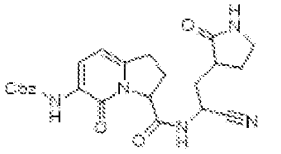

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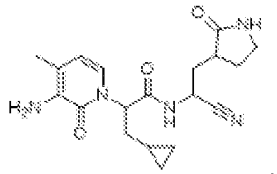

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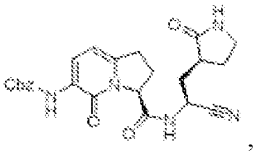

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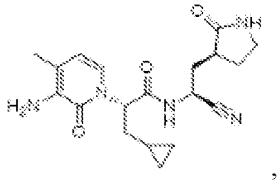

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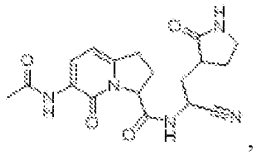

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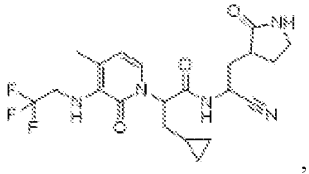

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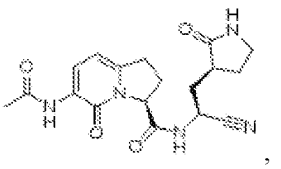

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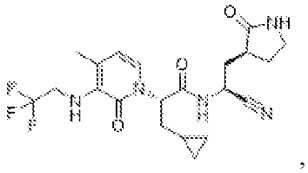

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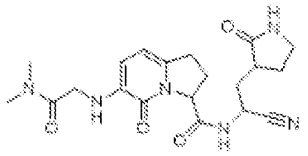
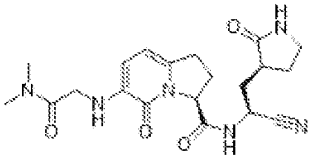
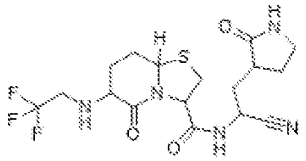
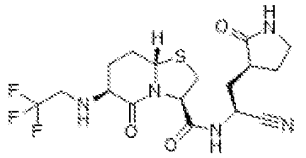
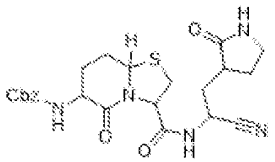
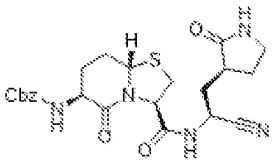
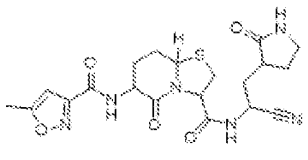
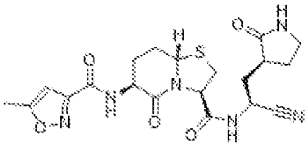
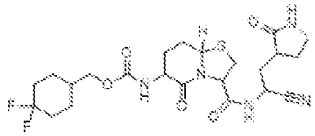
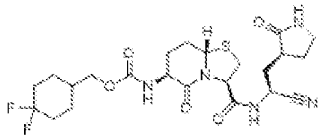
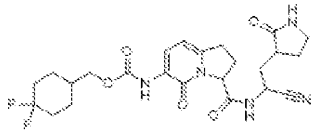
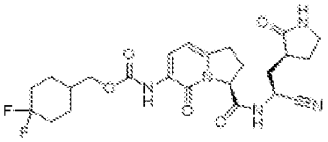
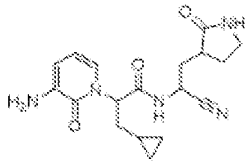
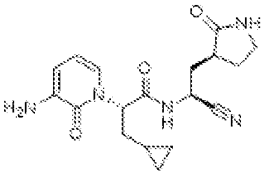
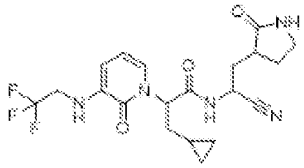
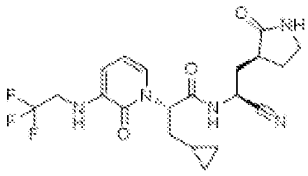

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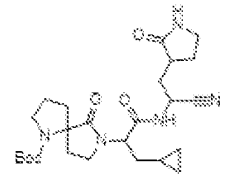

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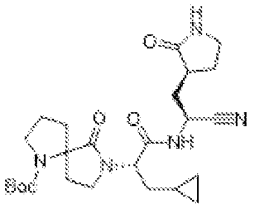

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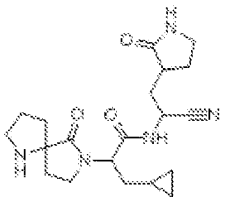

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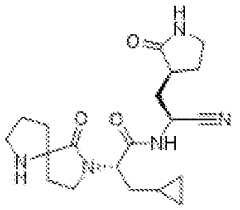
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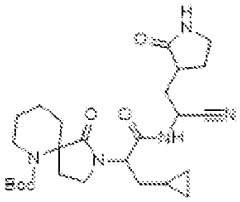
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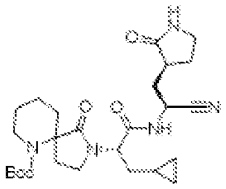
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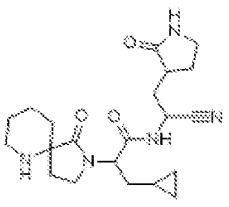
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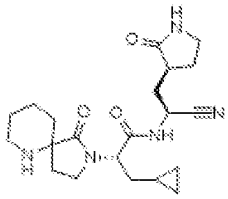
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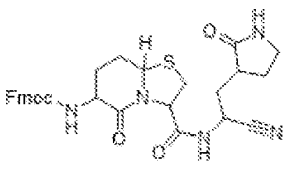
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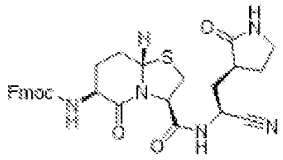
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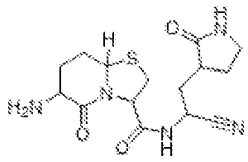
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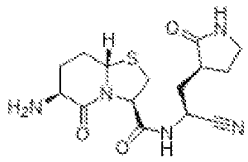
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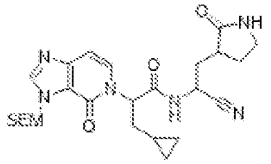
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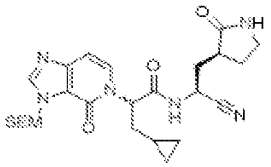
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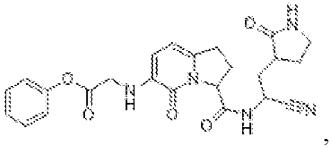
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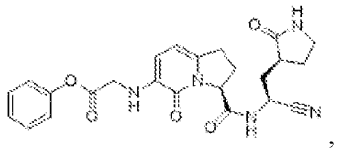
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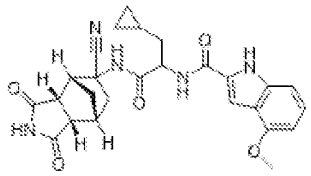
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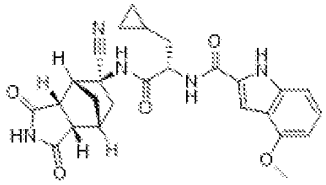
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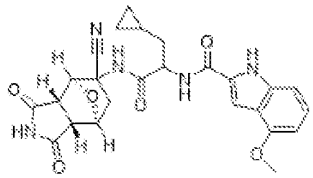
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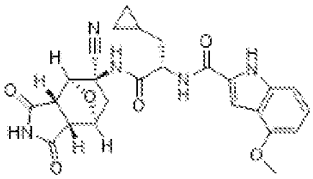
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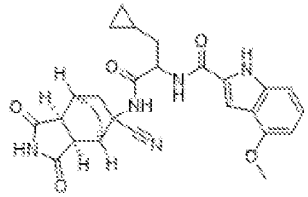
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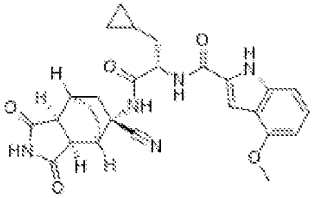
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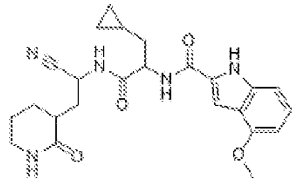
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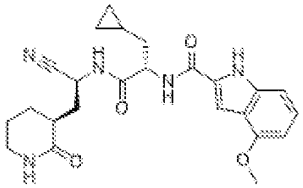
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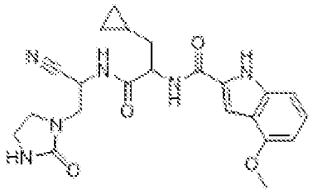
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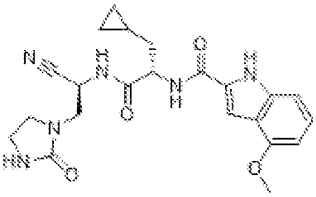
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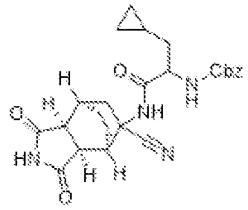
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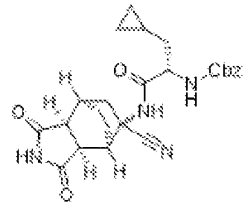
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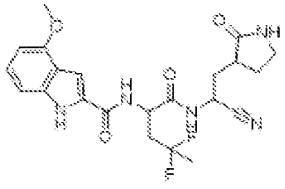
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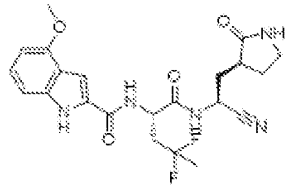
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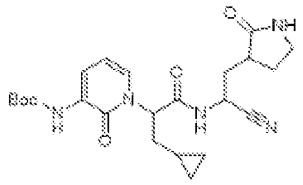
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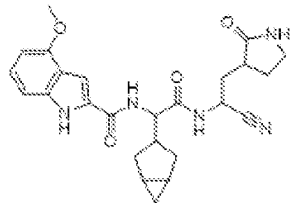
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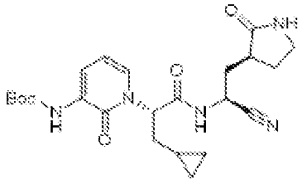
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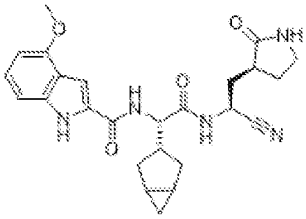
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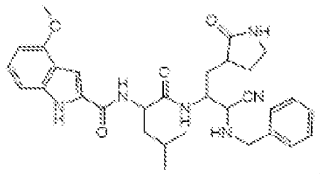
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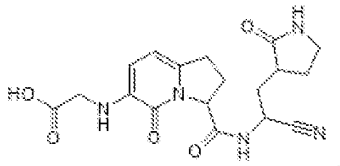
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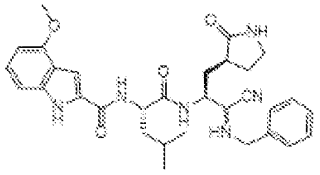
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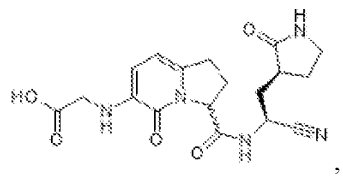
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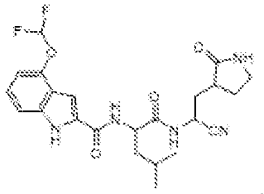
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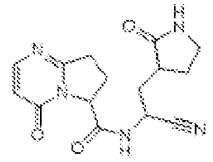
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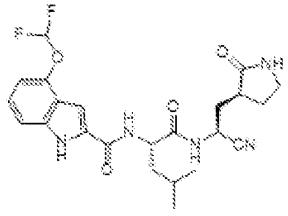
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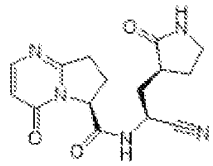
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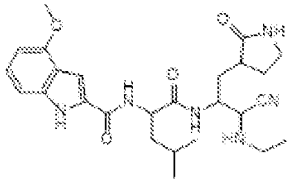
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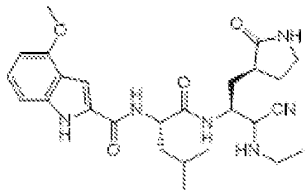
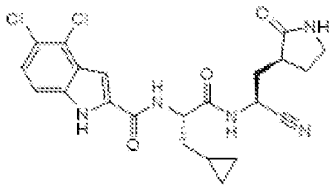
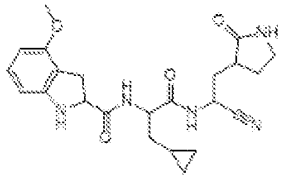
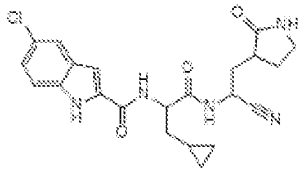
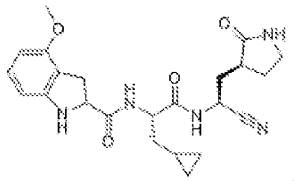
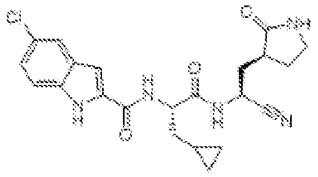
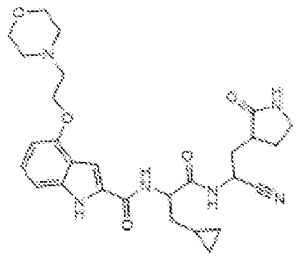
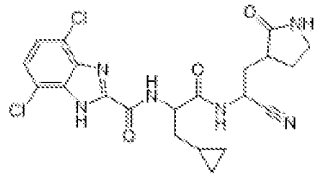
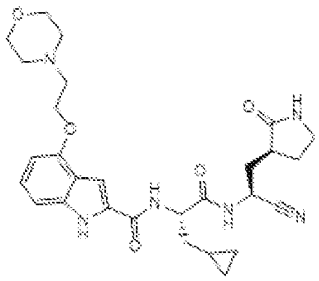
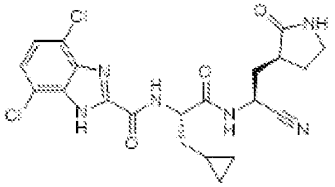
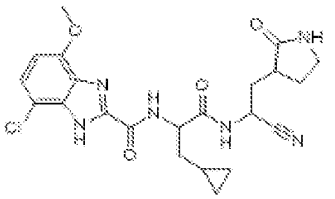
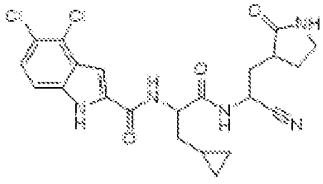
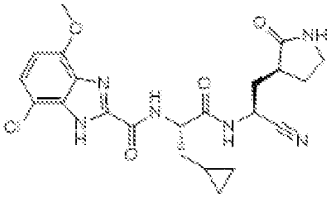
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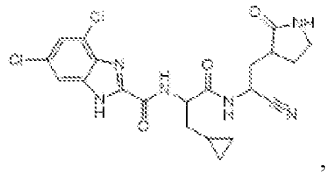


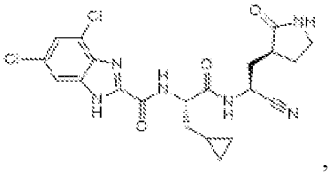
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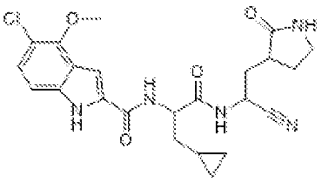


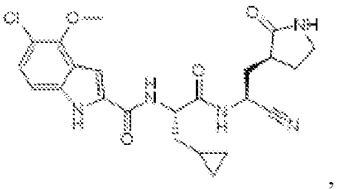
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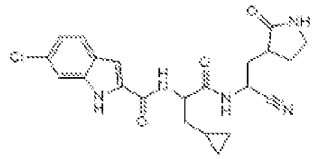

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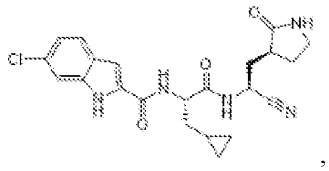

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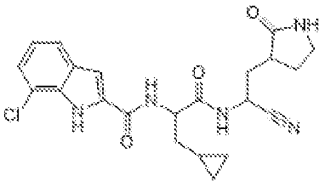

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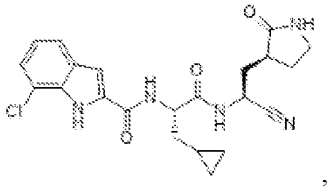

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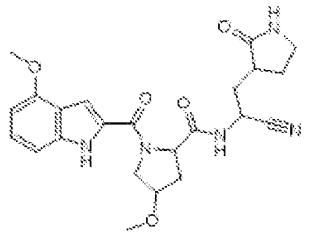

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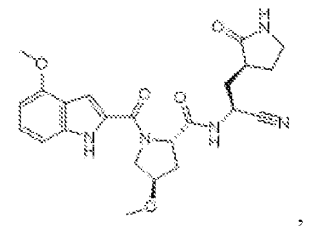

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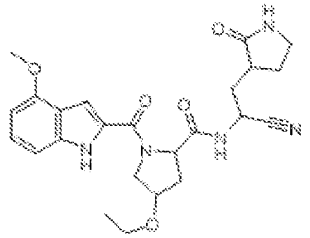

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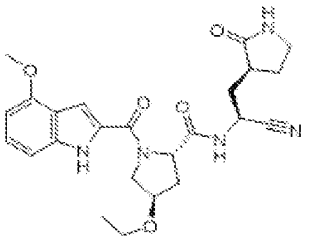

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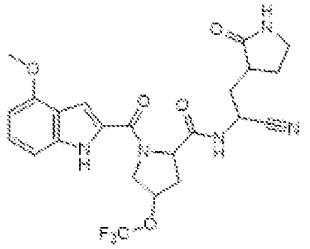

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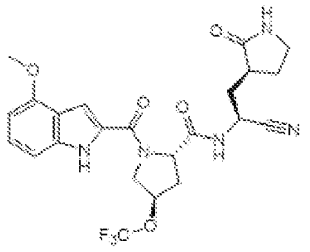

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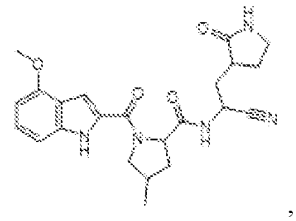

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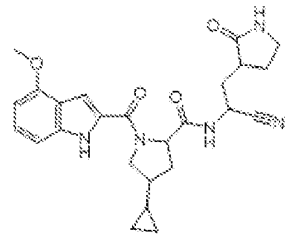

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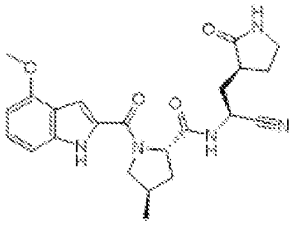

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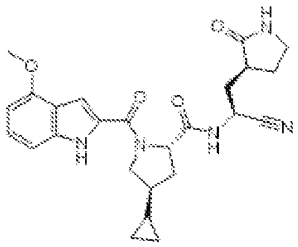
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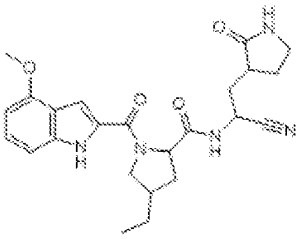
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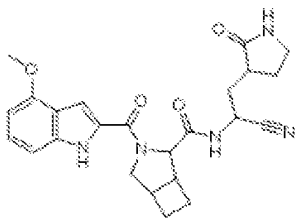
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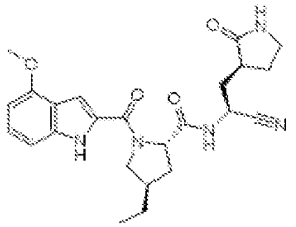
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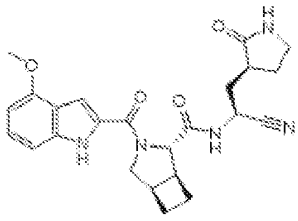
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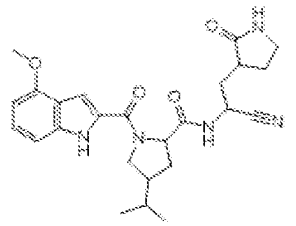
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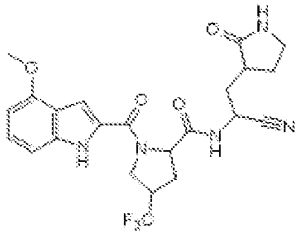
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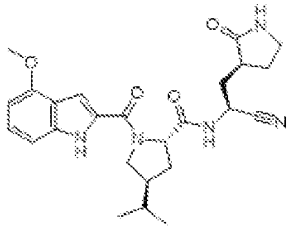
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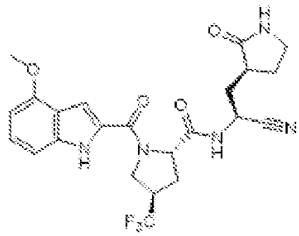
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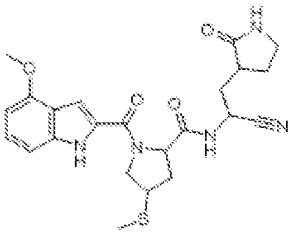
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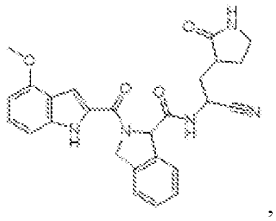
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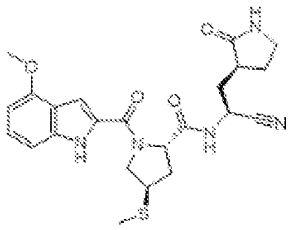
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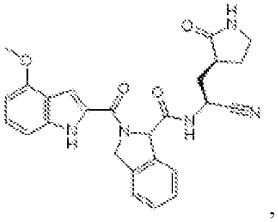
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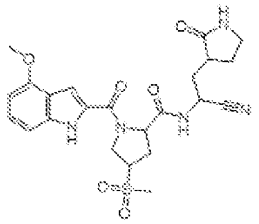
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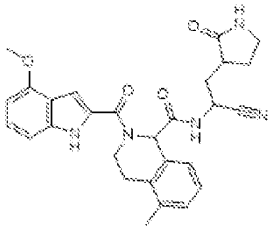
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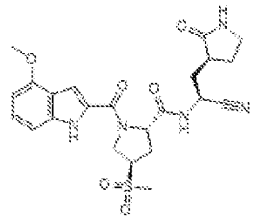
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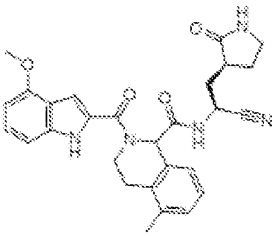
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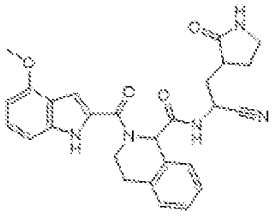
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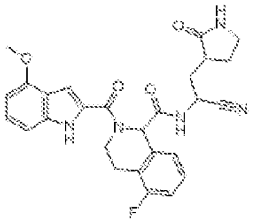
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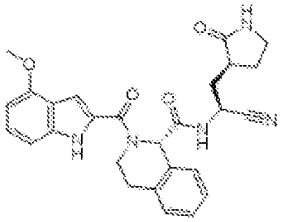
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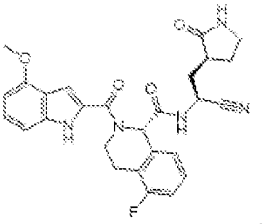
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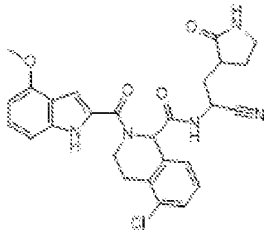
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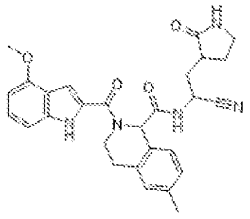
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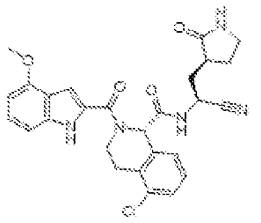
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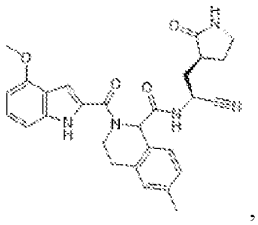
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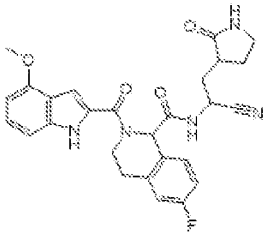
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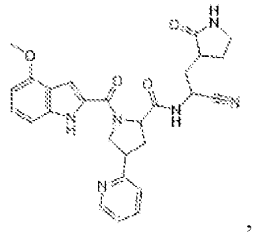
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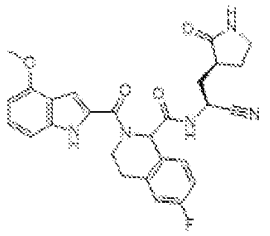
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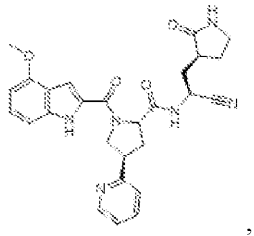
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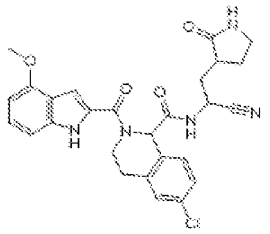
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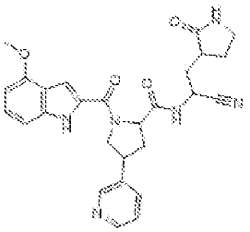
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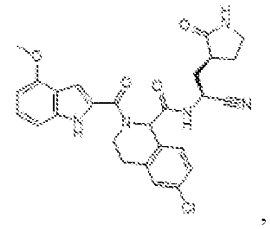
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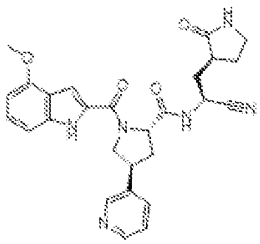
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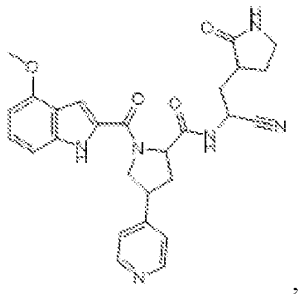
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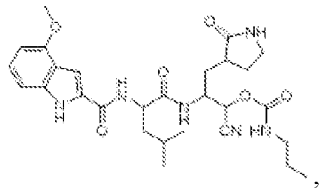
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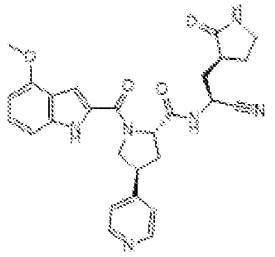
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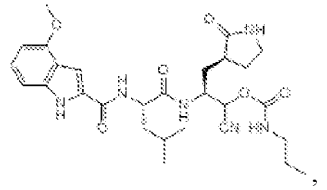
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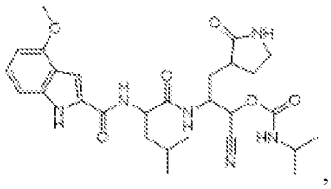
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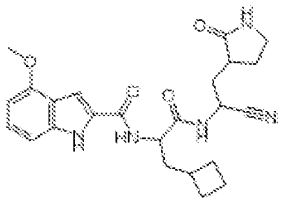
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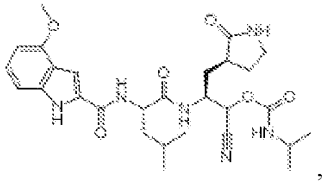
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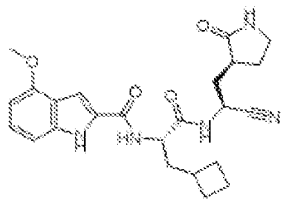
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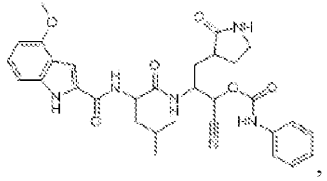
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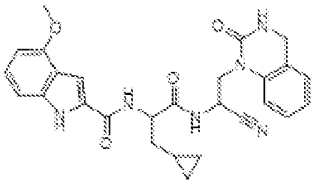
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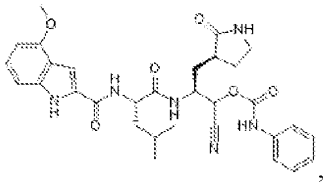
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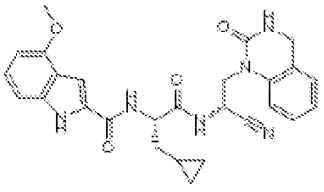
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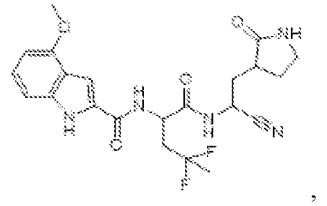
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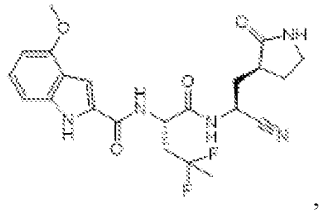
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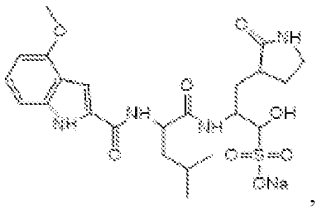
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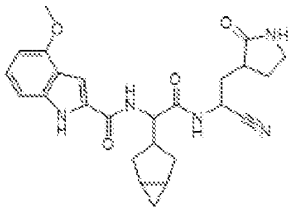
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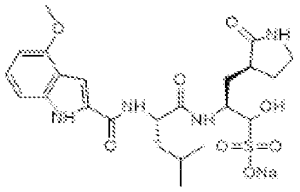
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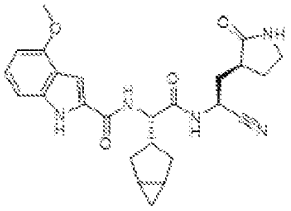
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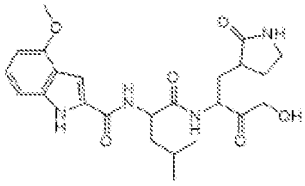
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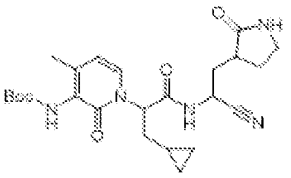
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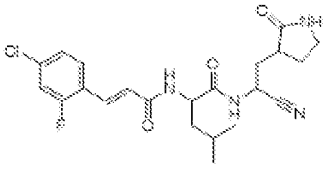
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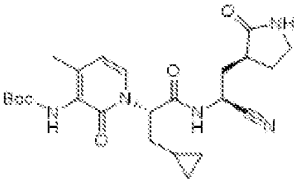
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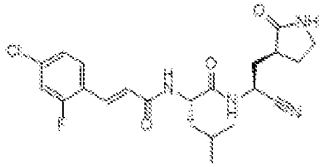
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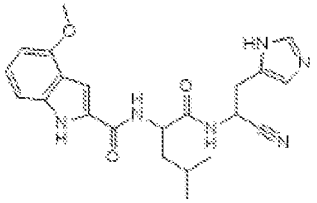
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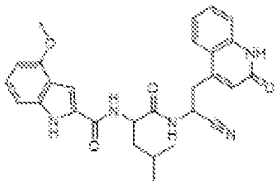
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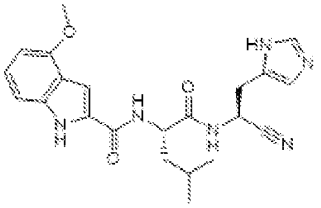
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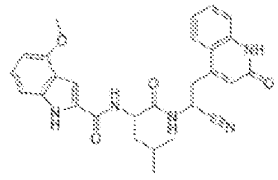
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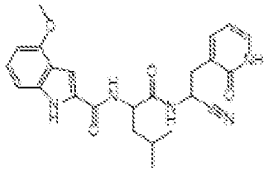
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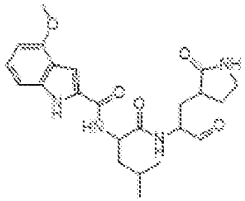


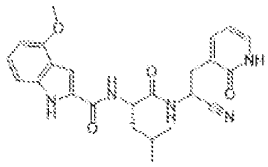
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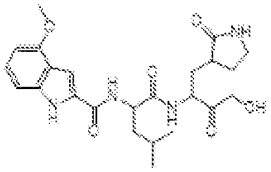


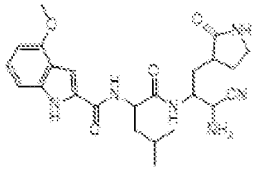
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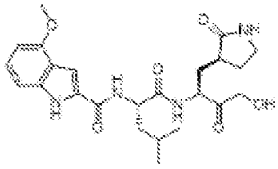

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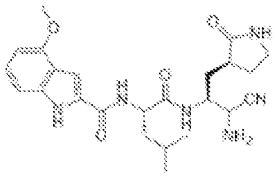

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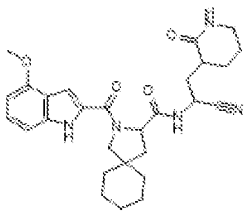

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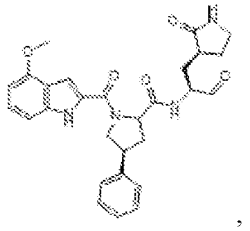

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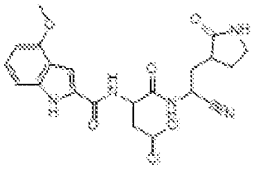

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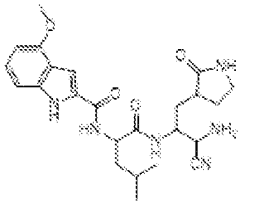

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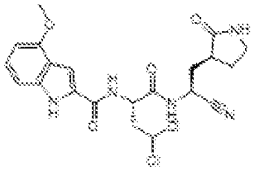

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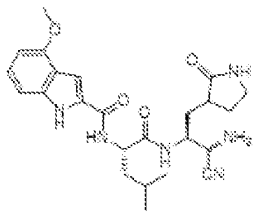

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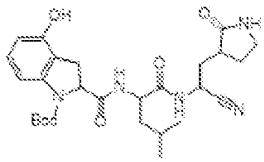

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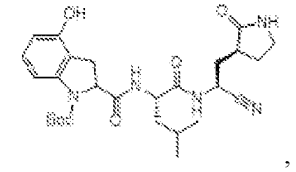

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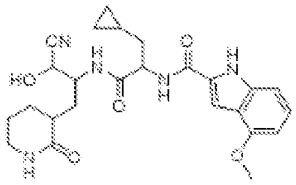

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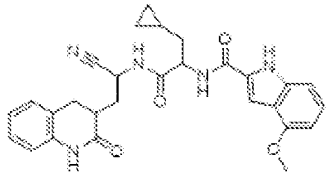

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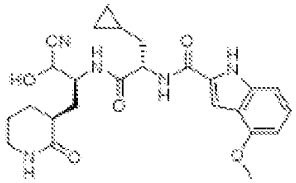
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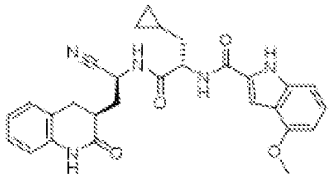
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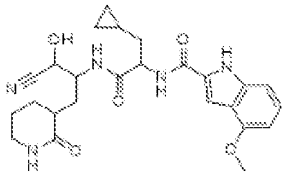
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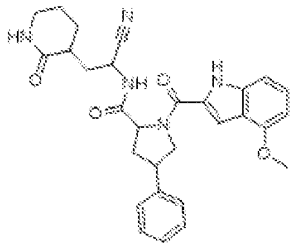
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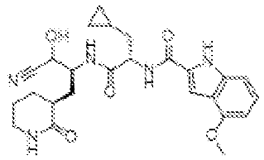
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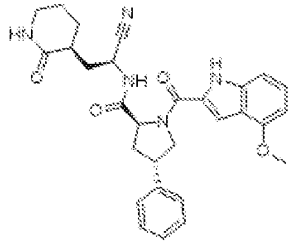
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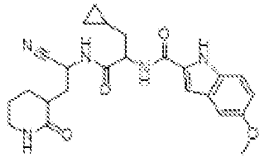
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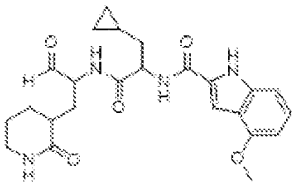
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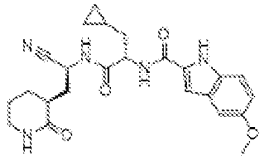
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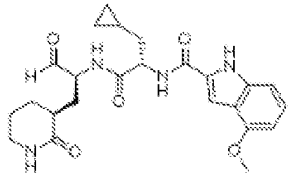
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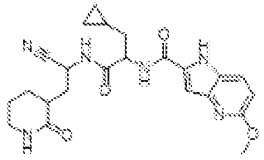
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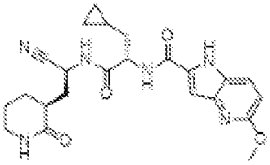


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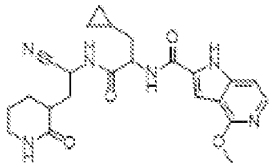


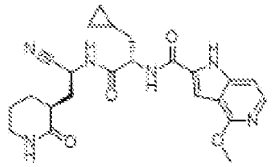
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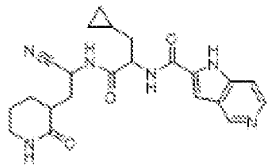
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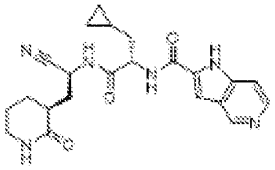


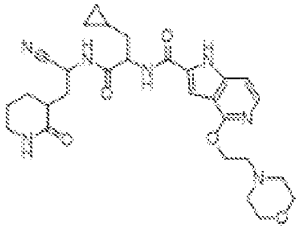
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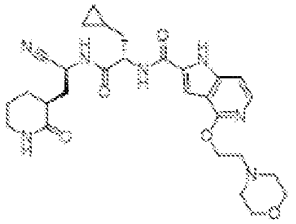

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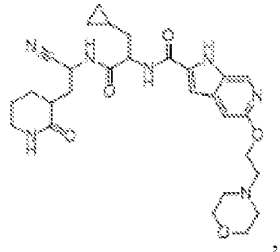

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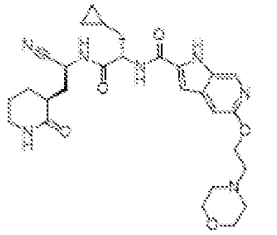

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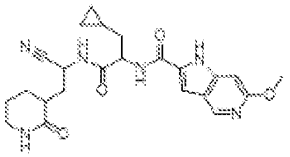

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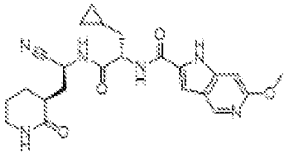

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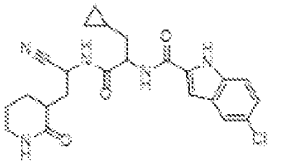

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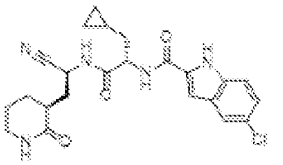

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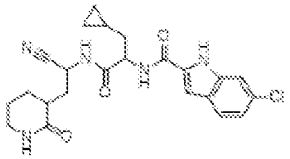

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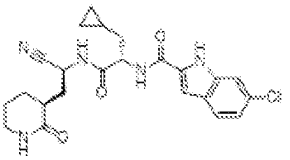

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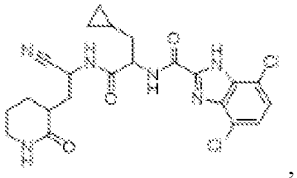

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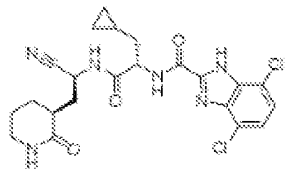

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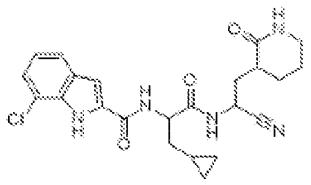

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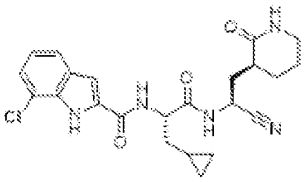

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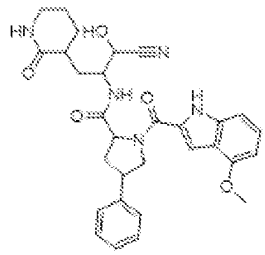
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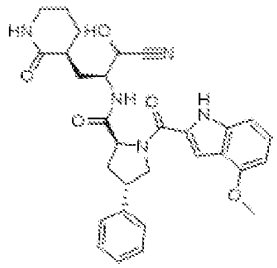
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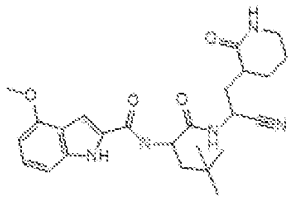
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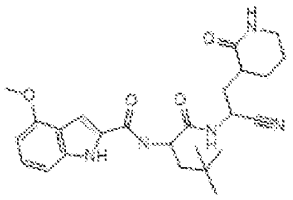
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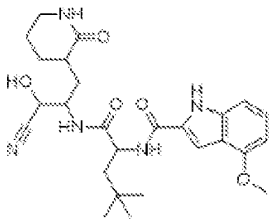
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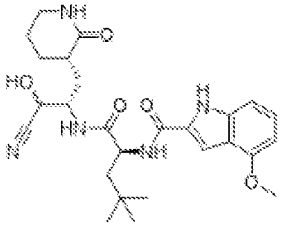
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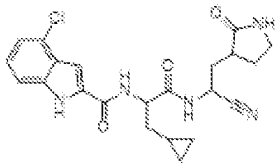
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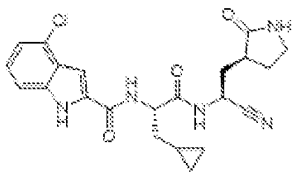
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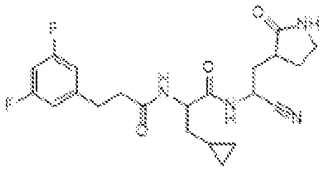
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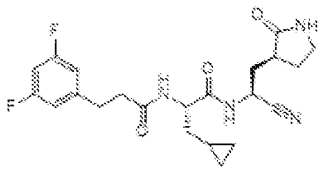
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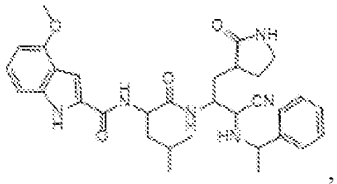
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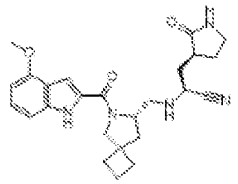
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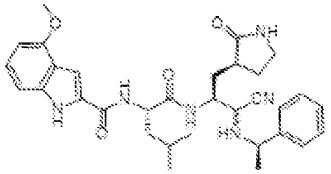
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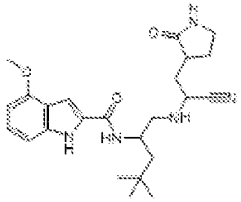
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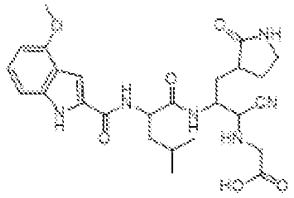
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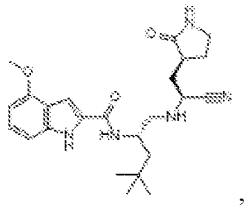
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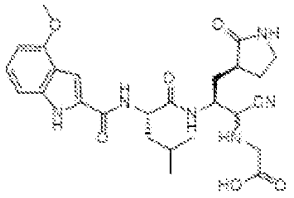
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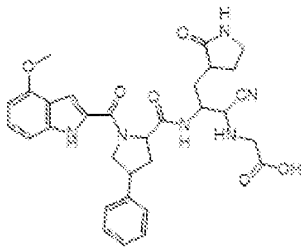
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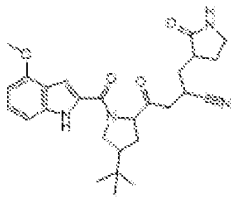
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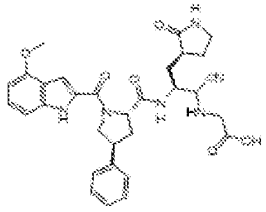
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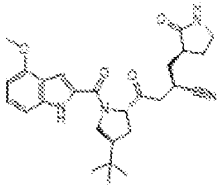
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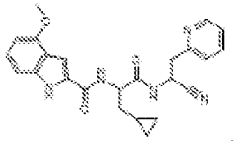
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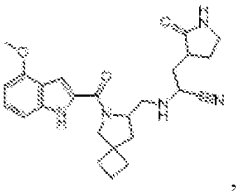
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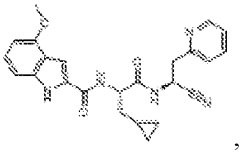
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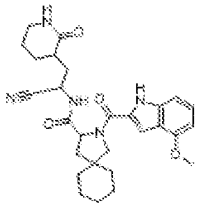
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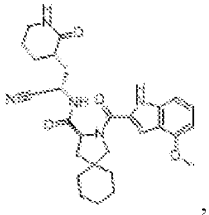
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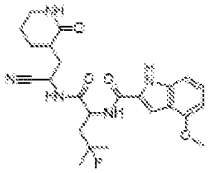
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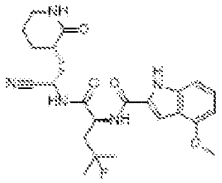
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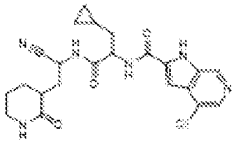
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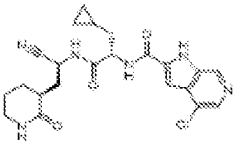
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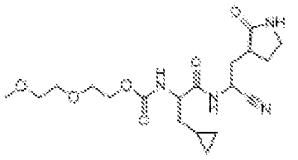
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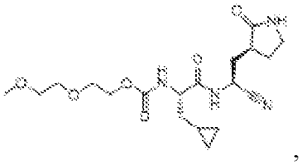
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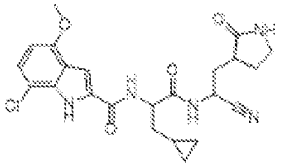
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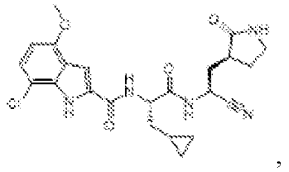
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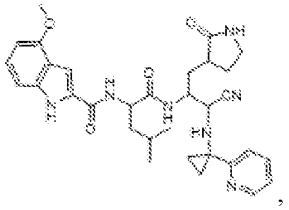
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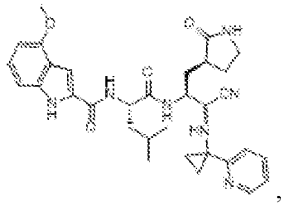
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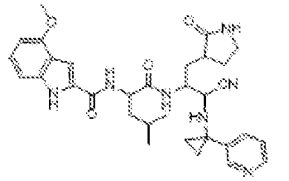
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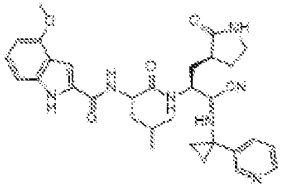
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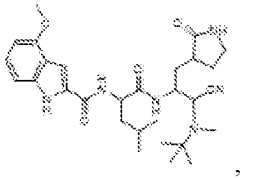
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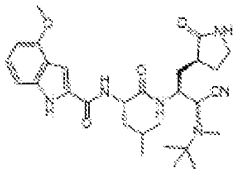
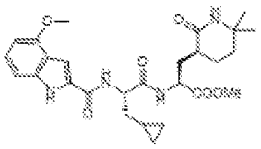
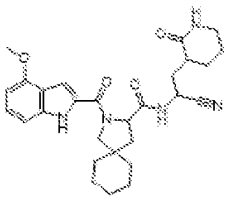
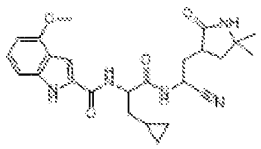
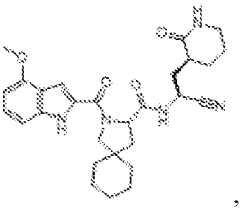
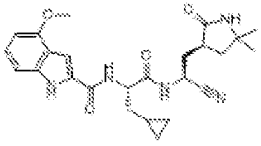
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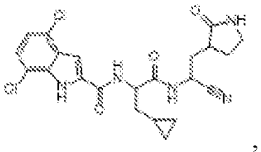
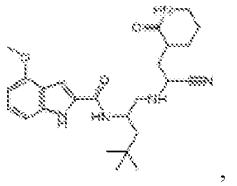
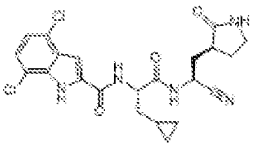
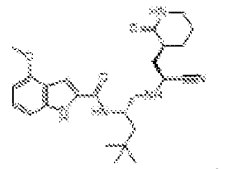
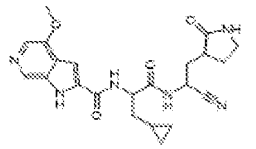


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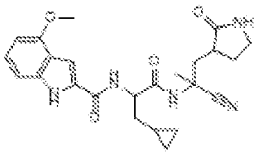
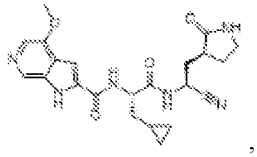
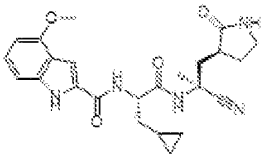
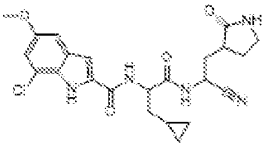
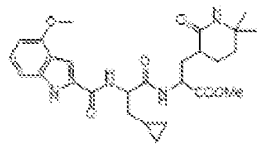
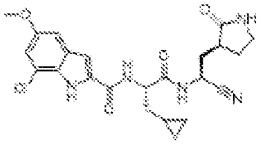


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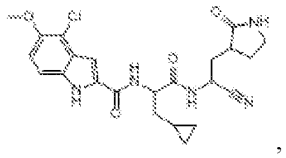
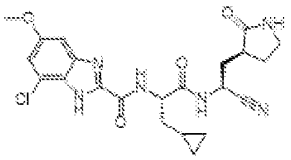
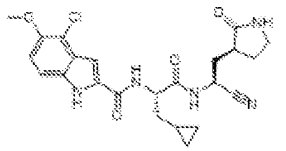
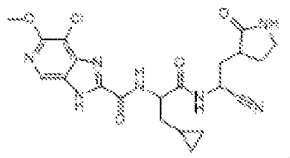
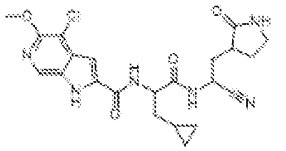
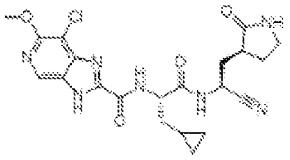
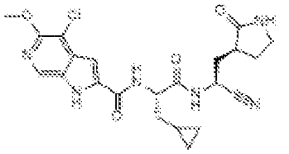
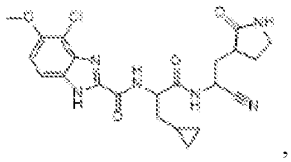
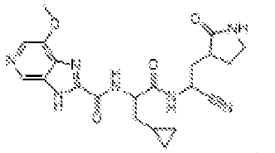
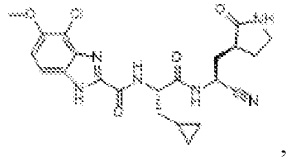
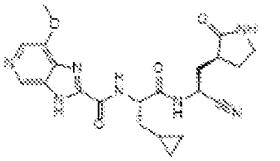
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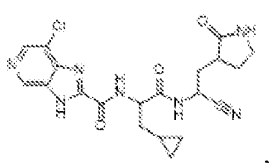
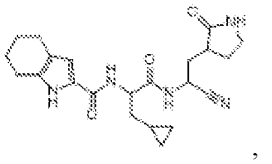
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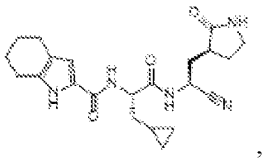
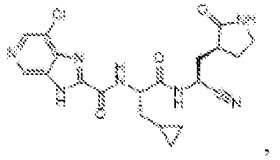
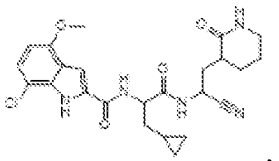
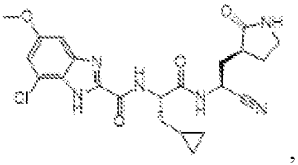
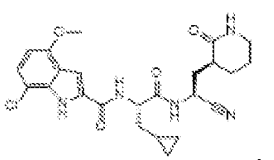
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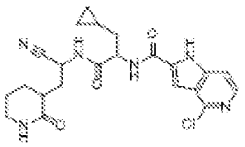
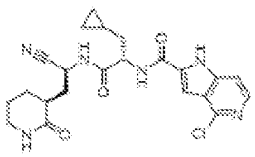
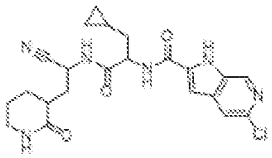
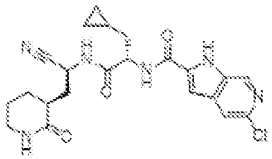
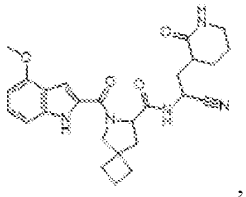
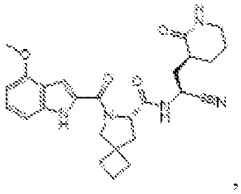
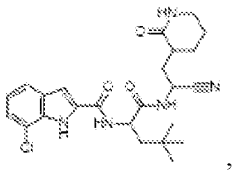
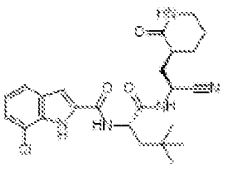
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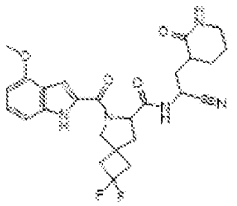
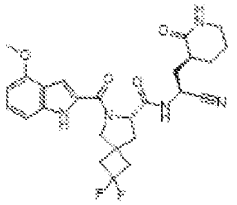
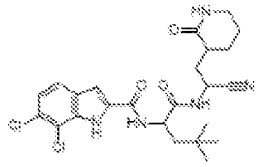
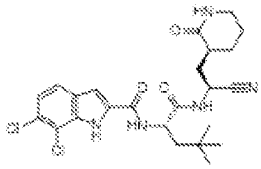
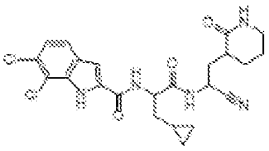
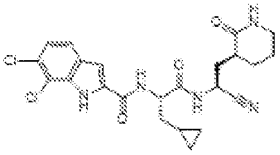
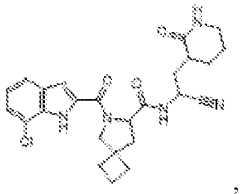
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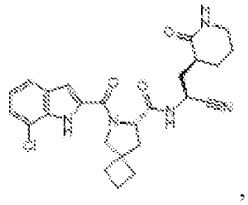

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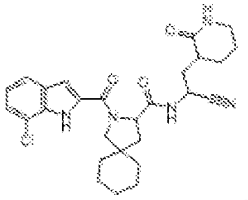
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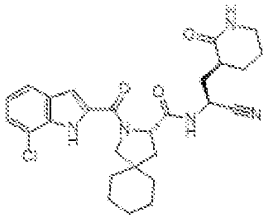
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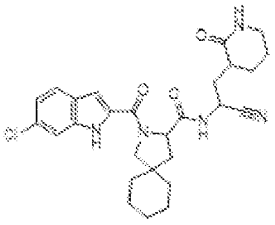
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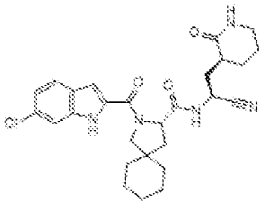
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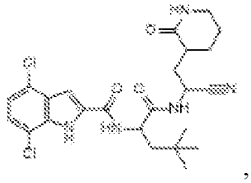
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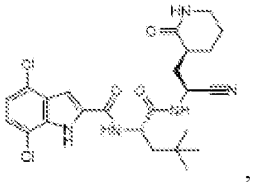
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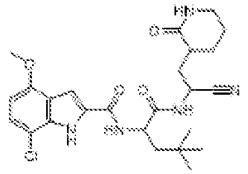
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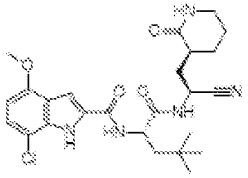
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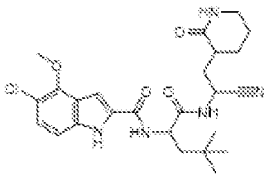
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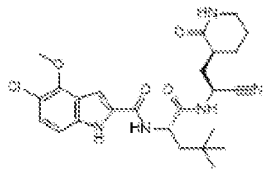
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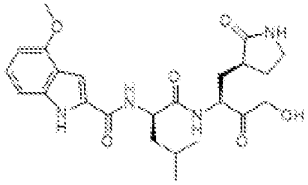
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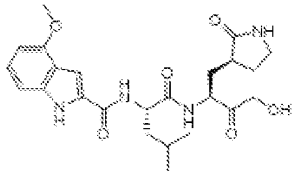
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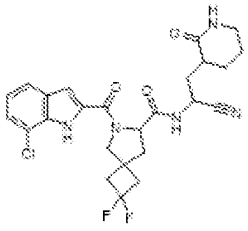
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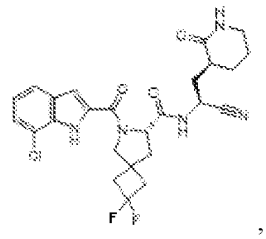
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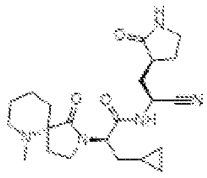
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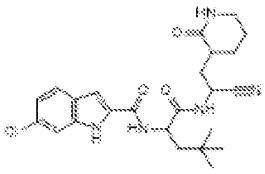
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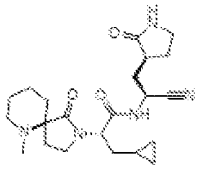
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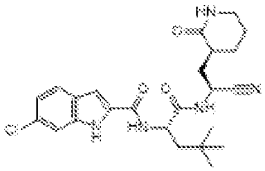
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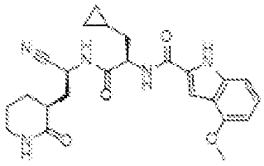
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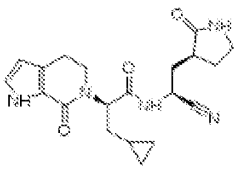
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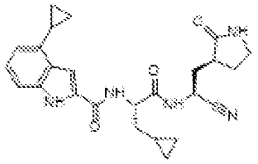
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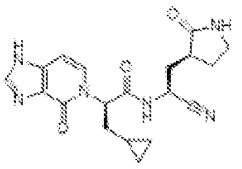
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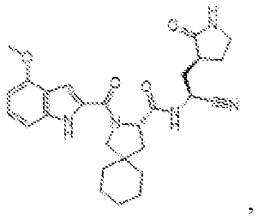
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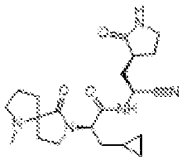
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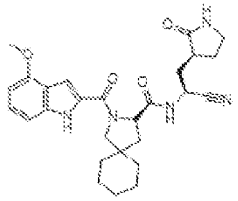
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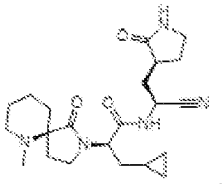
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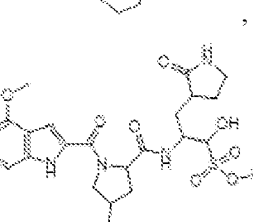
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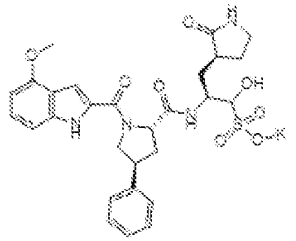


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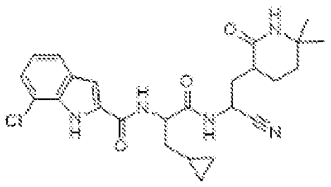


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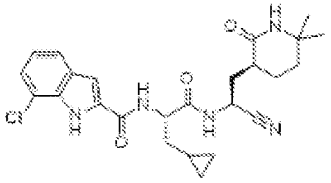
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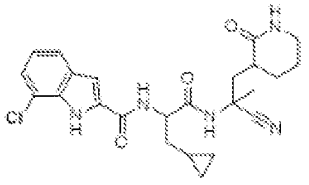
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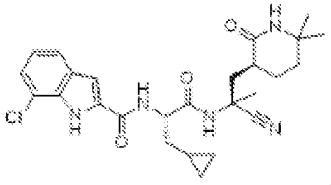
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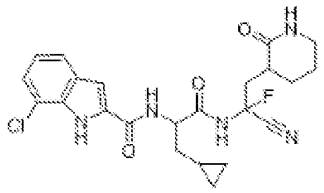
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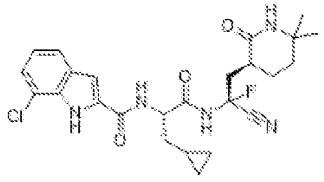
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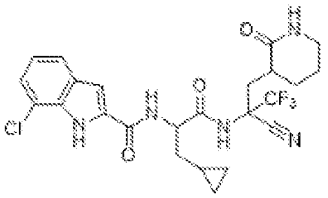
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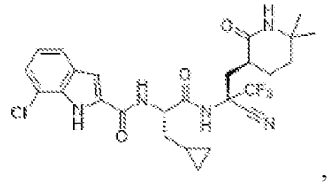
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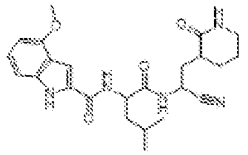
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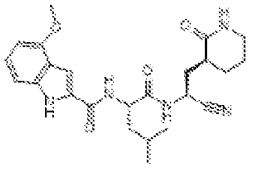
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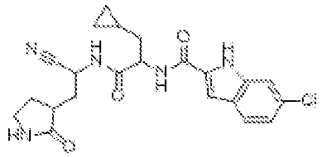
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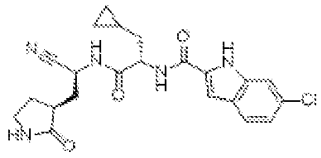
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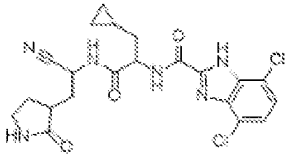
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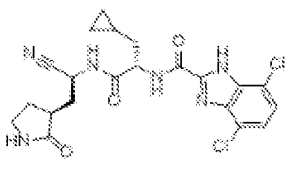
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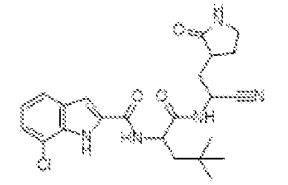
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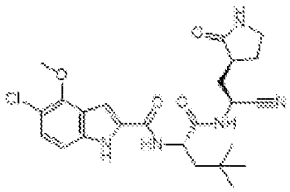
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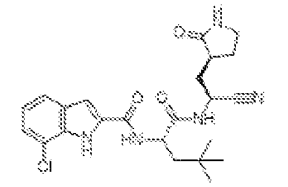
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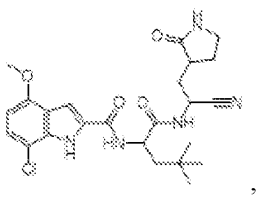
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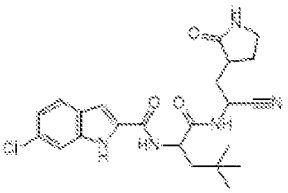
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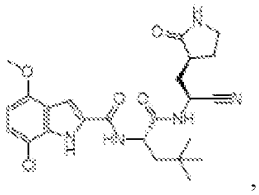
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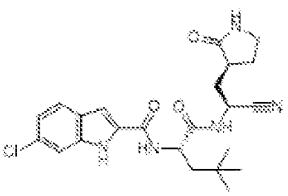
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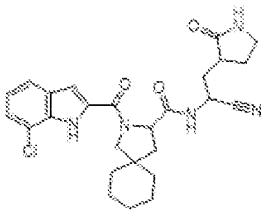
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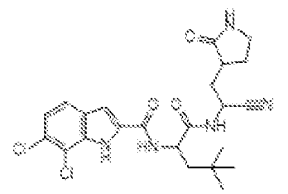
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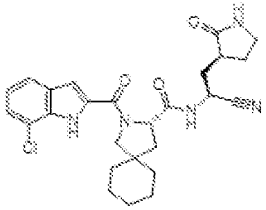
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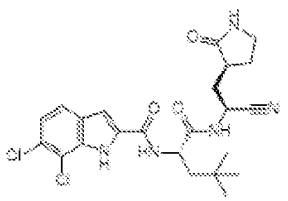
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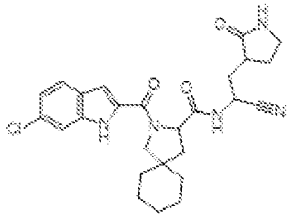
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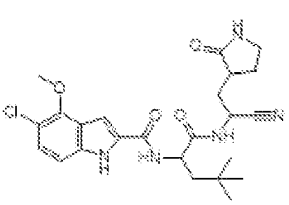
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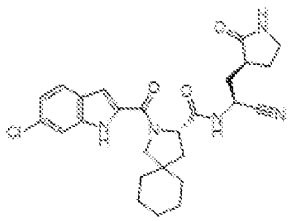
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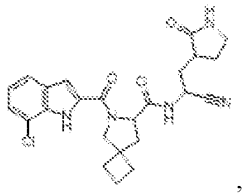
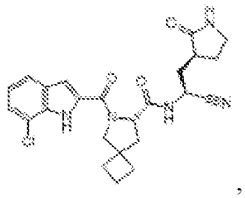
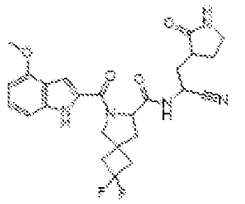
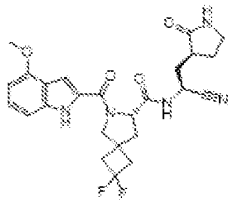
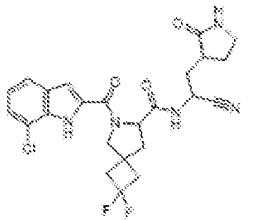
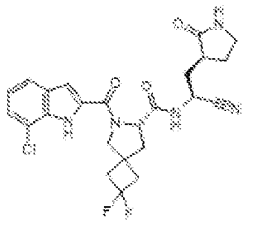
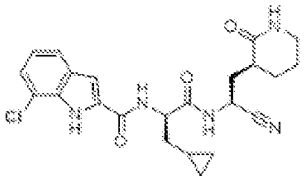
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17. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds of the embodiment.

18. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
19. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus,

murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.

20. The viral infection is a coronavirus infection.
21. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).
22. The viral infection is SARS-CoV-2.
23. The viral infection is an arenavirus infection.
24. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.
25. The viral infection is an influenza infection.
26. The influenza is influenza H1N1, H3N2 or H5N1.
27. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of any compound of the embodiment to a patient suffering from the virus, and/or contacting an effective amount of any compound of the embodiment with a virally infected cell.
28. The method further comprises administering another therapeutic.
29. The method further comprises administering an additional anti-viral therapeutic.
30. The anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir,

pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.

31. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

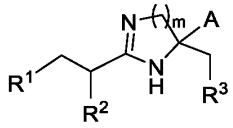
32. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.

33. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of any compound of the embodiment.
34. The compound is administered before viral exposure.
35. The compound is administered after viral exposure.

6. Contemplated Embodiment

[000195] In another aspect, the compositions, compounds and methods of the present disclosure may be described in another embodiment as follows:

1. A protease inhibitor compound represented by:



Formula I,

wherein:

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NH_2$, $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10 membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

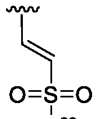
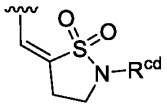
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a warhead;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

m is 1 or 2; and

pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

2. A is selected from the group consisting of cyano, –$C(O)R^D$, –$C(O)CH_2N(R^bR^c)$, –$C(O)CH_2OC(O)R^D$, –$C(O)C(O)R^D$, –$(CH=CH)C(O)OR^D$, –$(CH=CCN)C(O)OR^D$, –$(CH=CCN)C(O)(NH)R^D$, –CH(CN)(OH), -$CH(CN)(NR^bR^c)$,  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} –$N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

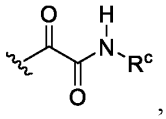
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

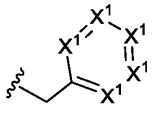
R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -$N(R^bR^c)$, wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl,

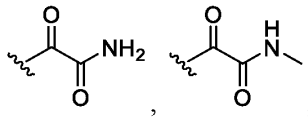
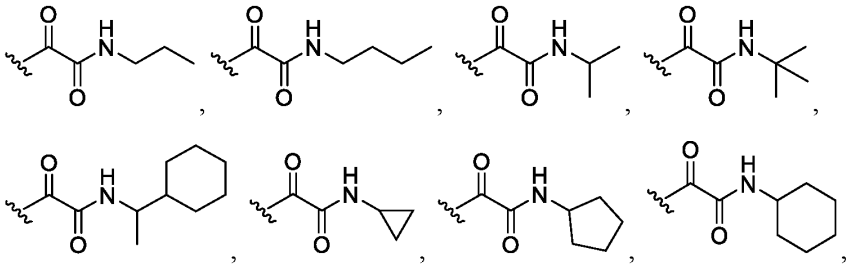
and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

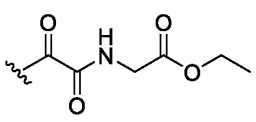
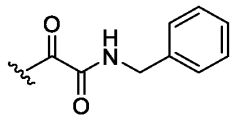
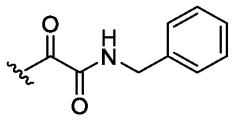
R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

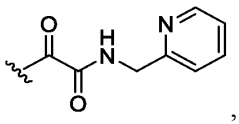
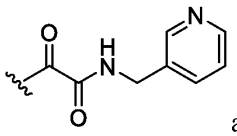
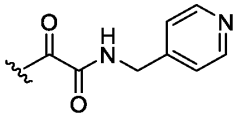
R^b and R^c are each selected from the group consisting of hydrogen, $–CH_2C(O)O(C_1$-C_8alkyl), $–C(O)$-$(C_1$-C_8alkyl), $–S(O)_2$-$(C_1$-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -$(C_1$-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

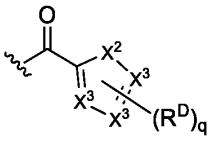
3. A is a warhead represented by:  , wherein R^c is selected from the group consisting of hydrogen, $–CH_2C(O)O(C_1$-C_8alkyl), C_1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

4. R^c is  , wherein X^1 is independently selected, for each occurrence, from N and CH.

5. A is selected from the group consisting of  , 

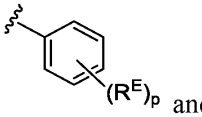
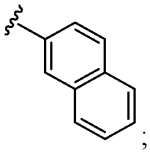
 ,  ,  ,

 ,  and  .

6. A is  , wherein

X^2 is selected from the group consisting of NH, O and S;

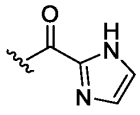
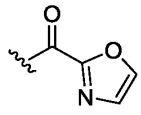
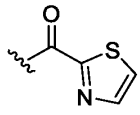
X^3 is independently selected, for each occurrence, from N and CH;

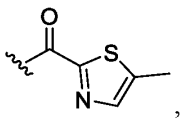
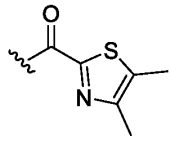
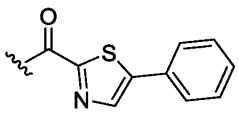
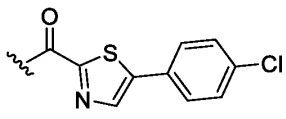
R^D is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl,  and  ;

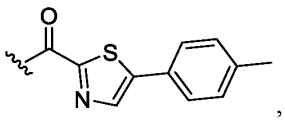
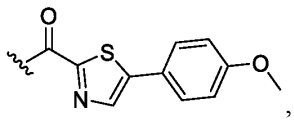
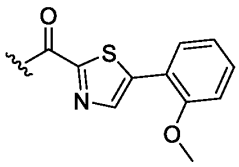
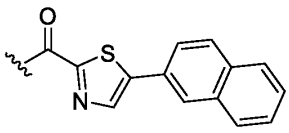
R^E is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, C_1-C_8alkyl and C_1-C_8alkoxy;

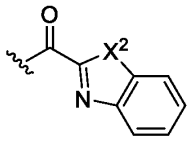
p is selected from 0, 1 and 2; and

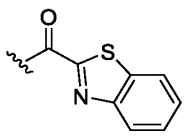
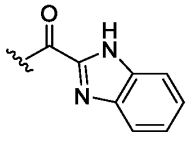
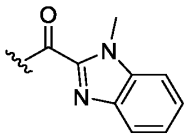
q is selected from 0, 1 and 2.

7. A is selected from the group consisting of  ,  ,  ,

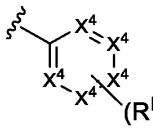
 ,  ,  ,  ,


,

,

and

.

8. A is  , wherein X^2 is selected from the group consisting of NH, NR^P, O and S, wherein R^P is C_1-C_8alkyl.

9. A is selected from the group consisting of  ,  and  .

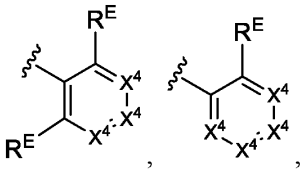
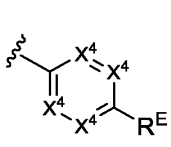
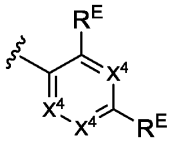
10. A is–$C(O)CH_2OC(O)R^D$, wherein

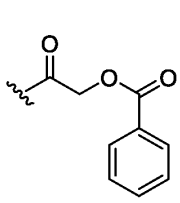
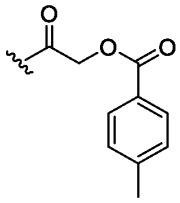
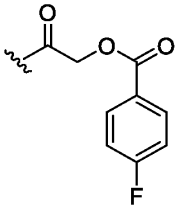
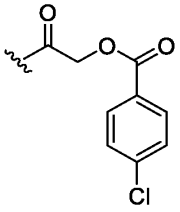
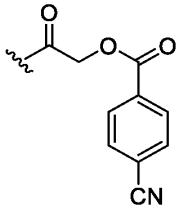
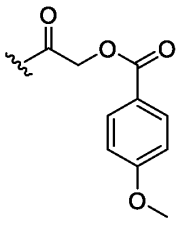
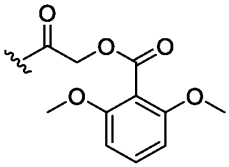
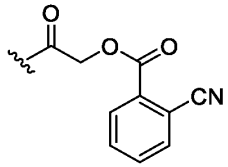
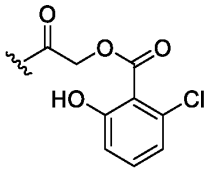
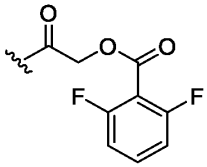
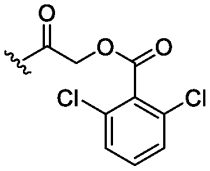
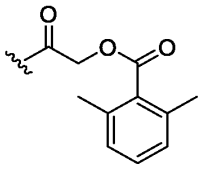
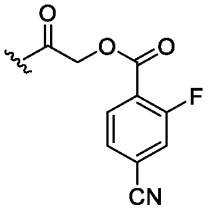
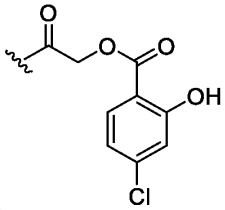
R^D is selected from the group consisting of  , C_1-C_8alkyl and C_3-C_6cycloalkyl;

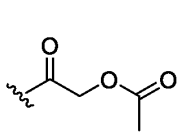
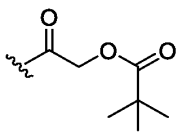
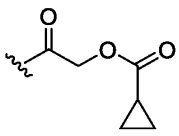
X^4 is independently selected, for each occurrence, from CH and N;

R^E is independently selected, for each occurrence, from the group consisting of halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-CF_3$, $-OCF_3$ and $-SCF_3$; and

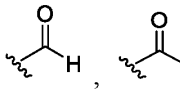
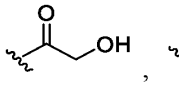
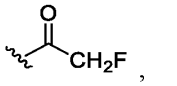
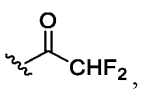
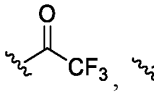
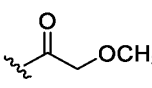
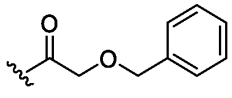
p is selected from 0, 1 and 2.

11. R^D is selected from the group consisting of  , ,  and  .

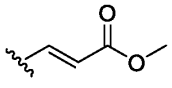
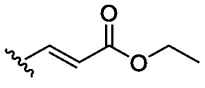
12. A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

13. A is selected from the group consisting of  ,  and  .

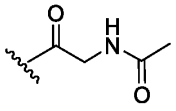
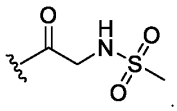
14. A is–C(O)R^D, wherein R^D is selected from the group consisting of hydrogen, –CH_2OH, -CH_2OR' and –CH_xF_y, wherein R' is selected from the group consisting of C_1-C_8alkyl, -(C_1-C_8alkyl)-(5-10 membered aryl), C_1-C_8heteroalkyl, C_3-C_6cycloalkyl and 5-10 membered aryl, wherein x is 0, 1 or 2; y is 1, 2 or 3; and the sum of x and y is 3.

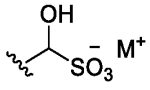
15. A is selected from the group consisting of  ,  ,  ,  ,  ,  and  .

16. A is –(CH=CH)C(O)OR^D, wherein R^D is C_1-C_8alkyl.

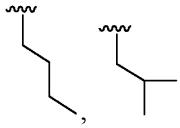
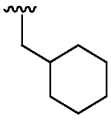
17. A is selected from  and  .

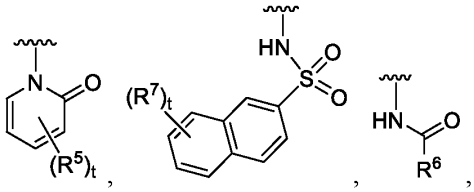
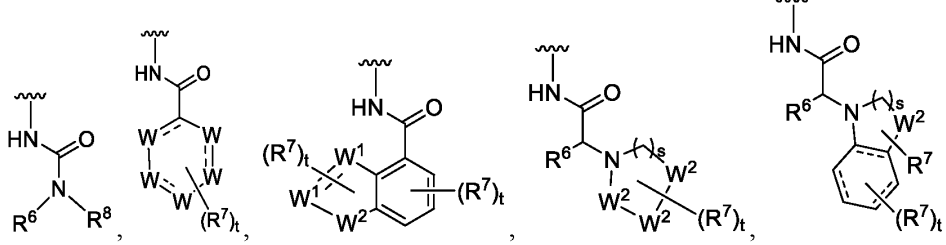
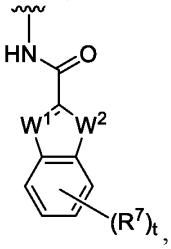
18. A is–$C(O)CH_2N(R^bR^c)$.

19. A is a warhead selected from  and  .

20. A is  , wherein M is selected from Na and K.

21. A is cyano.

22. R^1 is selected from the group consisting of  , ,  and  .

23. R^2 is selected from the group consisting of  ,  , and  , wherein

 denotes a bond that may be a single or double bond;

R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^6 is C_1-C_8alkyl;

R^7 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

R^8 is selected from the group consisting of 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

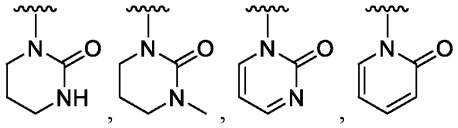
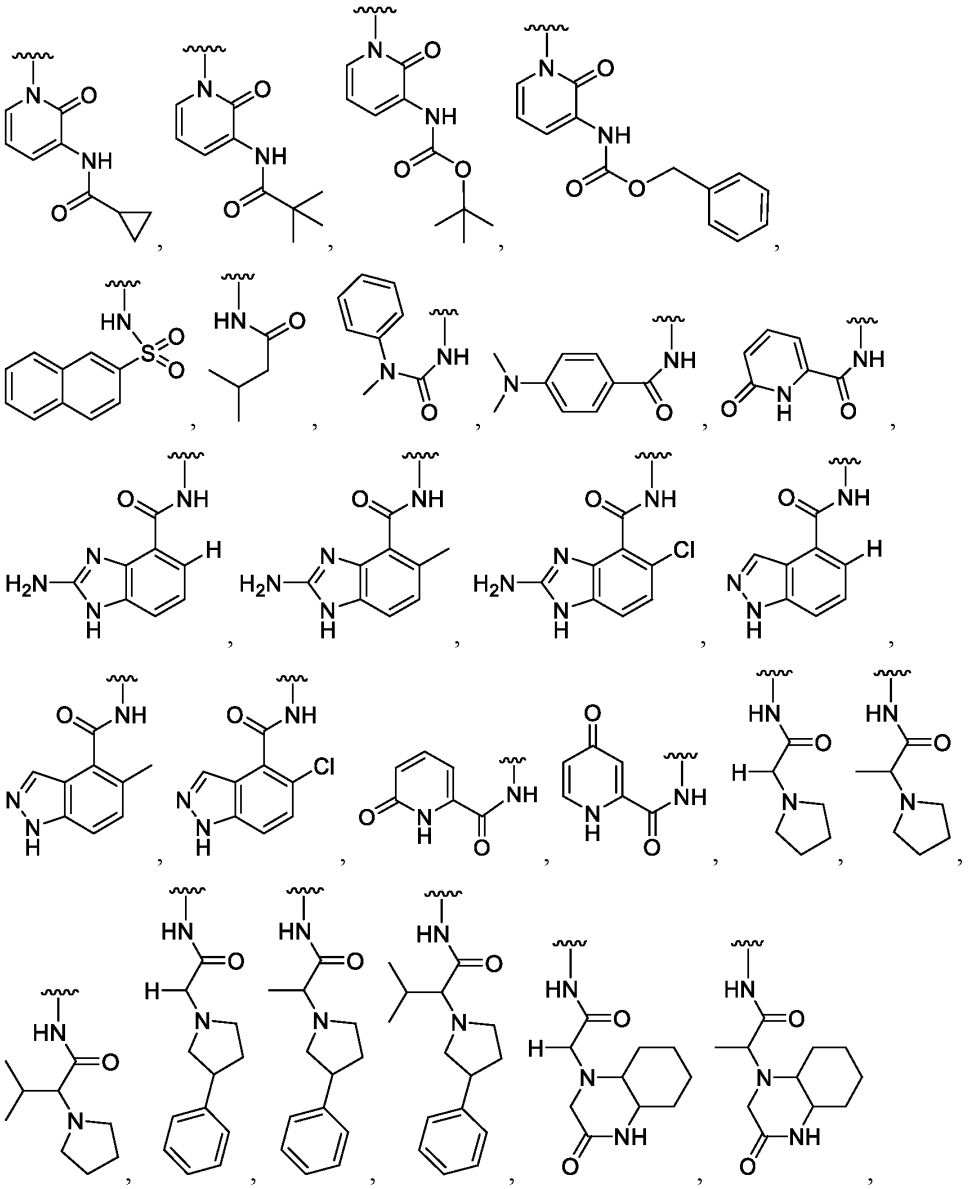
W^1 is selected from CH and N;

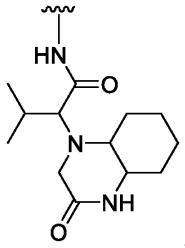
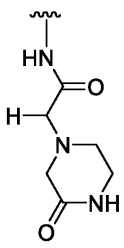
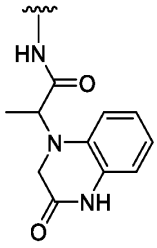
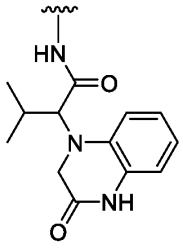
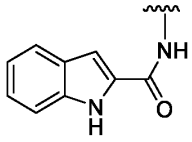
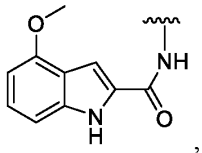
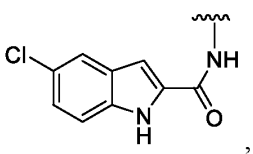
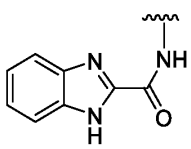
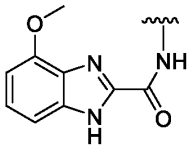
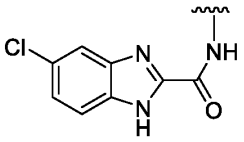
W^2 is selected from the group consisting of CH_2, O, NH and S;

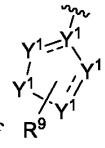
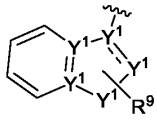
W is selected from W^1 and W^2;

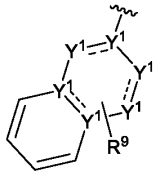
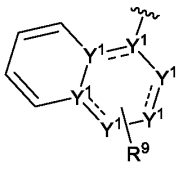
s is selected from 1 and 2; and

t is selected from 0, 1, 2 and 3.

24. R^2 is selected from the group consisting of  , 


,

,

,

,

,

,

,

,

and

.

25. R^3 is selected from the group consisting of

,

,

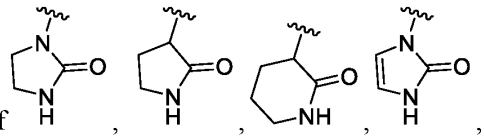
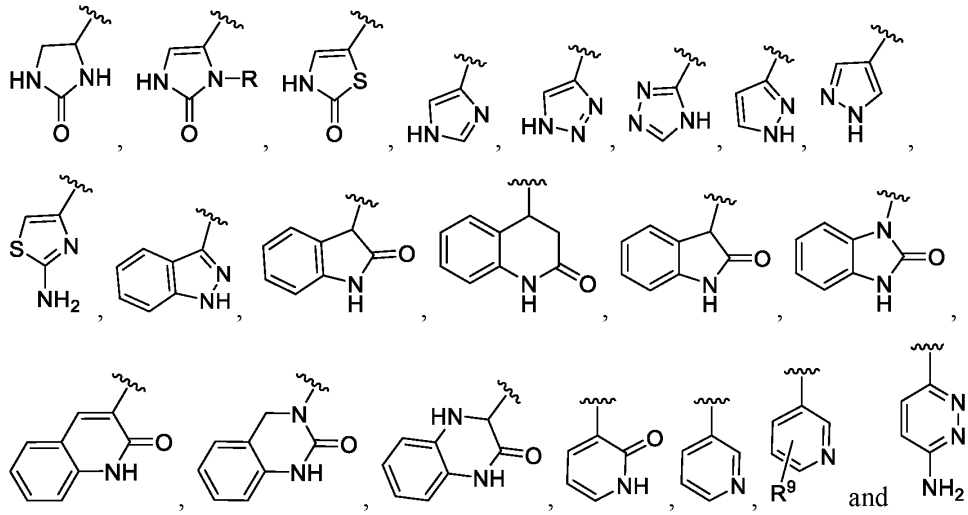
,

,

,

wherein

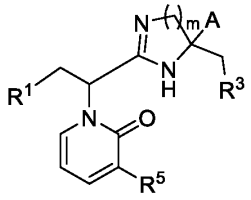
$=\!=\!=\!=\!=\!=\!=$ denotes a bond that may be a single or double bond;

Y^1 is selected from the group consisting of CH, CH_2, N, NH, O and S;

R^9 is selected from the group consisting of halogen, hydroxyl, oxo, $–NH_2$, $–N(CH_3)_2$, $–N(CH_2CH_3)_2$, $–CH_3$, $–CH_2CH_3$, $–OCH_3$ and $–OCH_2CH_3$.

26. R^3 is selected from the group consisting of  ,  , and .

27. The compound is represented by



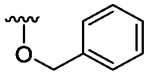
Formula I-A,

wherein:

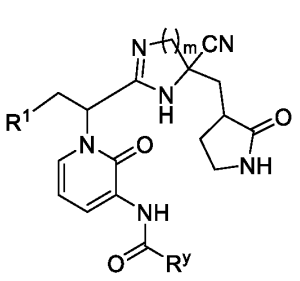
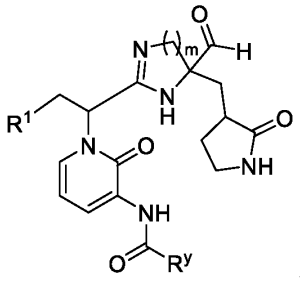
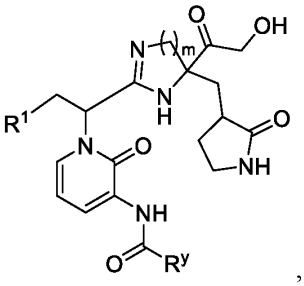
R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

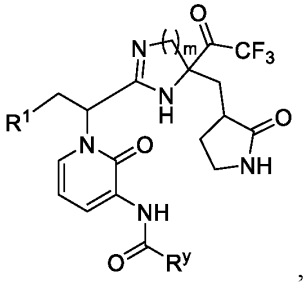
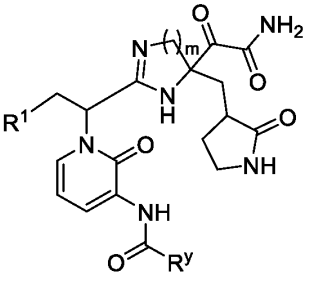
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl; and

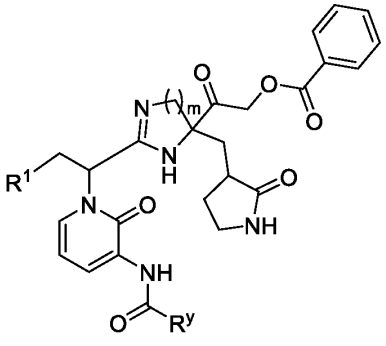
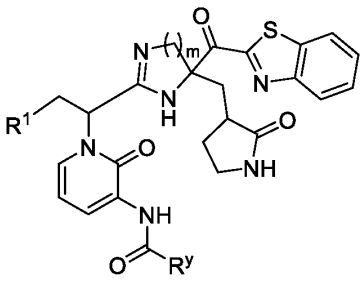
m is selected from 1 and 2.

28. R^y is selected from the group consisting of hydrogen,  ,  ,  and  .

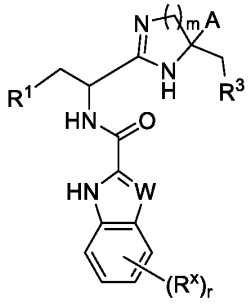
29. The compound is selected from the group consisting of:

 ,  ,  ,

 ,  ,

 , and  .

30. The compound is represented by



Formula I-B,

wherein

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

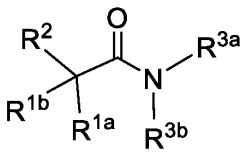
W is CH or N;

m is selected from 1 and 2; and

r is selected from 0, 1, 2 and 3.

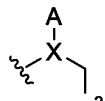
31. R^x is $-OCH_3$.

32. A protease inhibitor compound represented by:



Formula II,

wherein

R^{3a} is selected from  and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of C_1-C_8alkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl; or

R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–NH_2$, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocycle), –C(O)-O-(4-10 membered heterocycle), $–C(O)-OC(CH_3)_3$, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the alkyl, cycloalkyl, heterocycle, heteroaryl, or aryl may optionally be substituted by one, two or three substituents of halogen, C_1-C_6alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl or oxo;

R^2 is selected from the group consisting of –NHC(O)R^B, –NHC(O)N(R^B)$_2$, –NHC(O)C(R^C)$_2$$R^B$, –NHS(O)$_2$$R^B$, 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x; or

R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered mono or bicyclic heterocycle having a ring nitrogen, NR^G, or C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^G is selected from the group consisting of H, $C_{1\text{-}6}$alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m) and C(=O)-$C_{1\text{-}6}$alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl and heterocycle, wherein R^m is selected for each occurrence by H or $C_{1\text{-}3}$alkyl (optionally substituted by one, two or three fluorines), and C_3-C_6cycloalkyl (optionally substituted by one, two, or three fluorines);

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, SF_5, cyano, –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-

10 membered heterocycle, wherein the aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

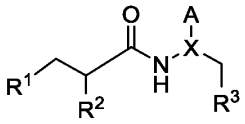
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a warhead;

X is selected from CH, $C(CH_3)$ and N; and

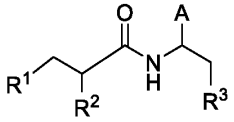
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

33. The compound is represented by:

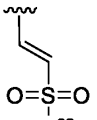
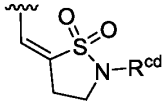


Formula II-A.

34. The compound is represented by:



Formula II-B.

35. A is selected from the group consisting of cyano, $–C(O)R^D$, $–C(O)CH_2N(R^bR^c)$, $–C(O)CH_2OC(O)R^D$, $–C(O)C(O)R^D$, $–(CH=CH)C(O)OR^D$, $–(CH=CCN)C(O)OR^D$, $–(CH=CCN)C(O)(NH)R^D$, –CH(CN)(OH), $-CH(CN)(NR^bR^c)$,  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} – $N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

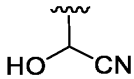
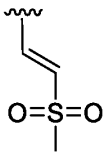
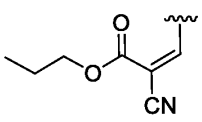
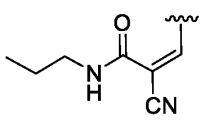
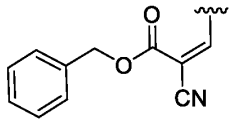
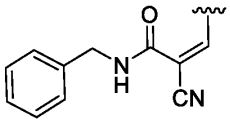
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

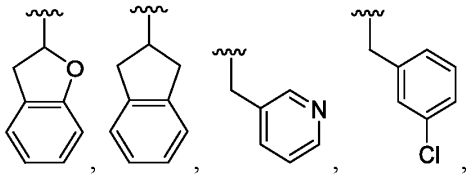
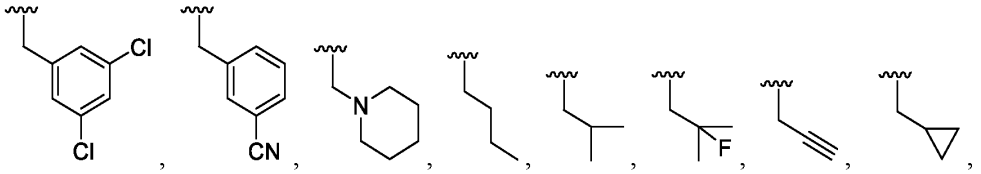
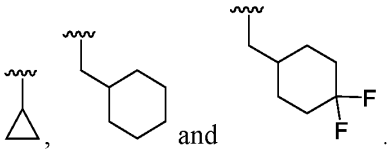
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -$N(R^bR^c)$, wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

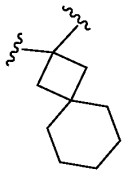
R^b and R^c are each selected from the group consisting of hydrogen, – $CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

36. A is selected from the group consisting of -CN,  ,  ,  ,  ,  , and  .

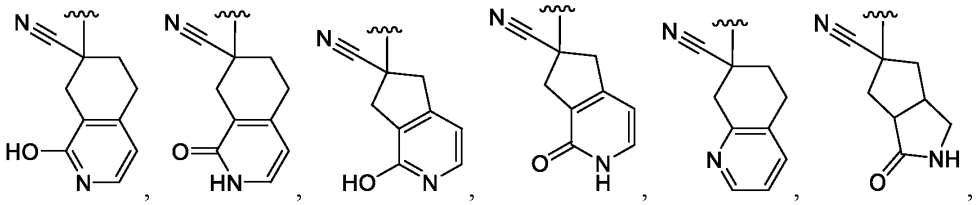
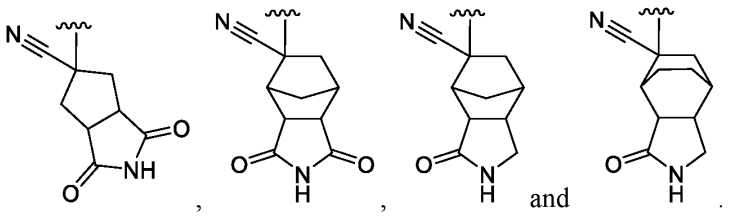
37. R^{1a} is selected from the group consisting of  ,  ,  and .

38. R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

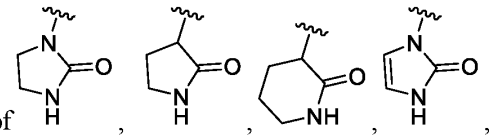
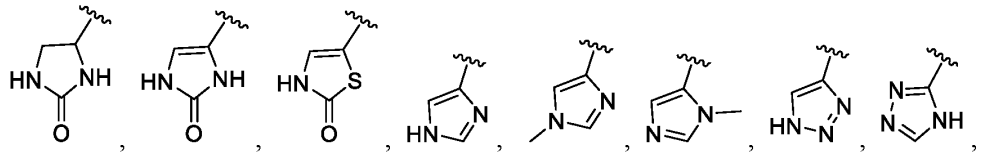
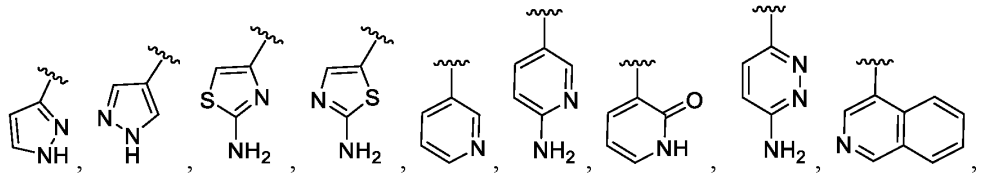
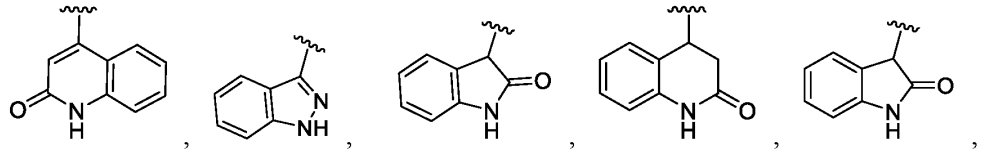
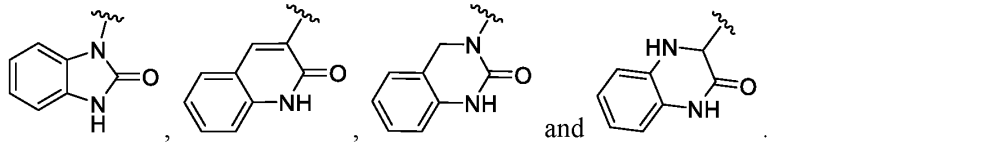
39. R^{1b} is hydrogen.

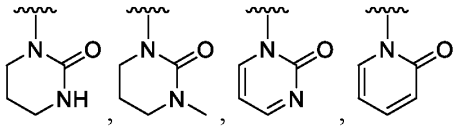
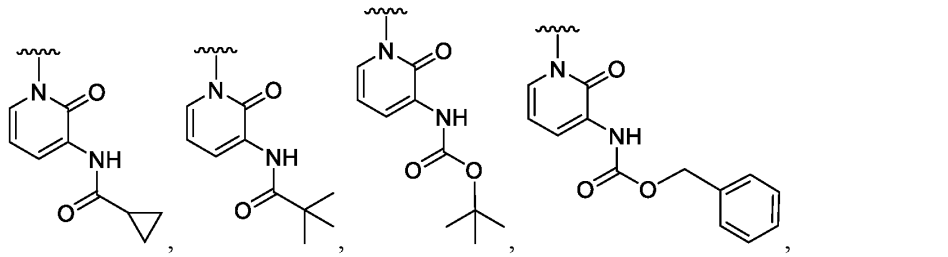
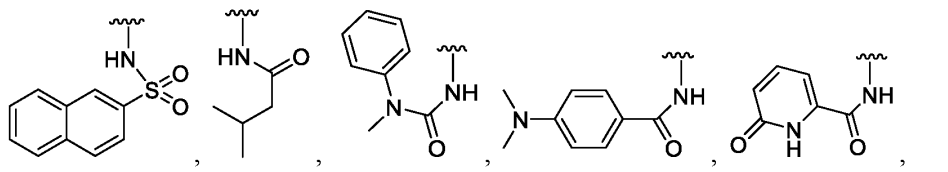
40. R^{1a} and R^{1b} are joined to together to form  .

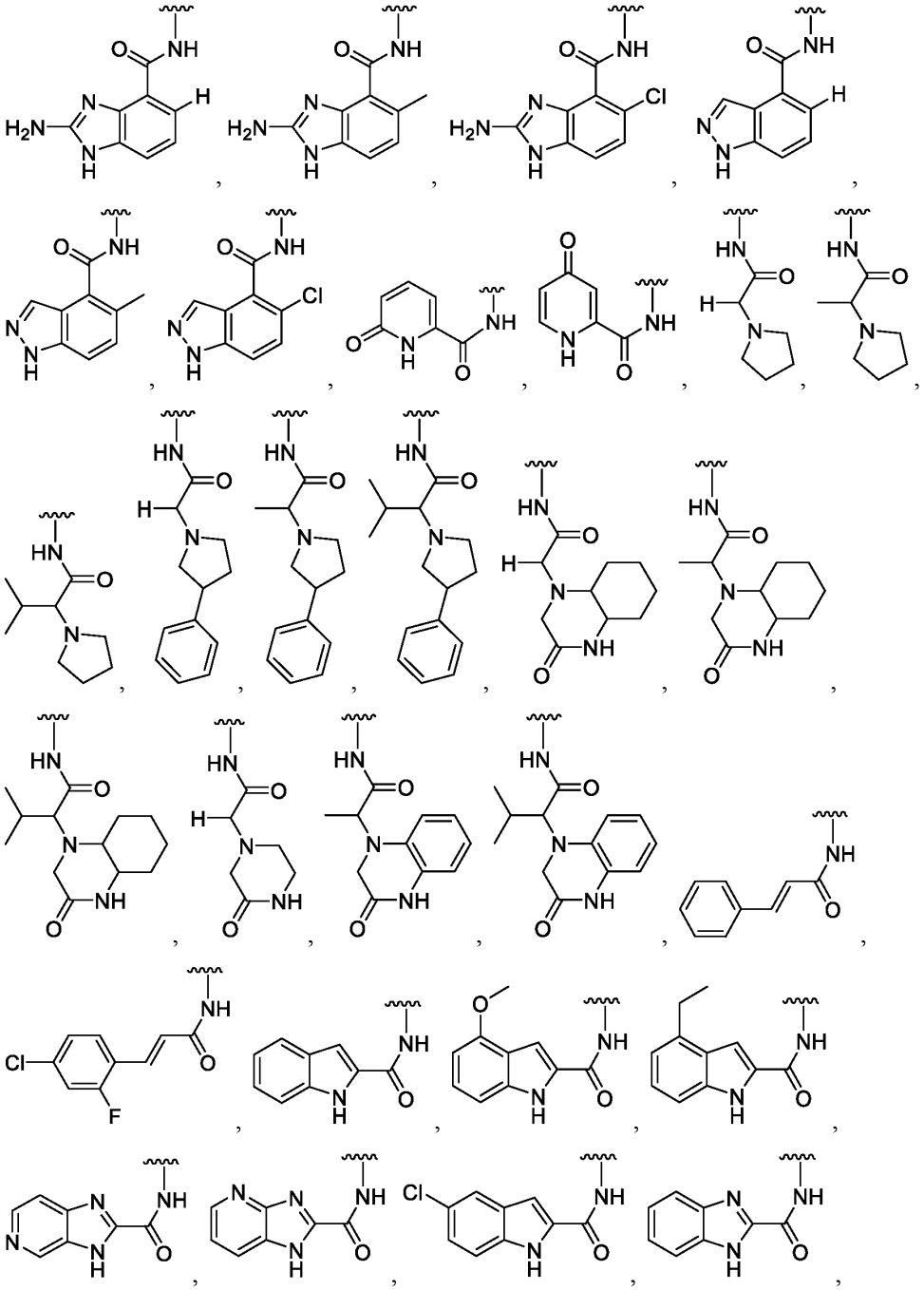
41. R^{3a} is a 4-10 membered heterocycle substituted by A.

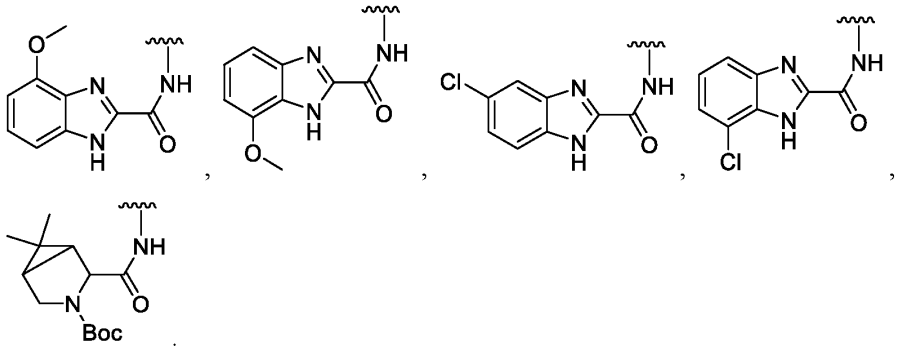
42. R^{3a} is selected from the group consisting of  ,  and .

43. R^3 is a 4-10 membered heterocycle.

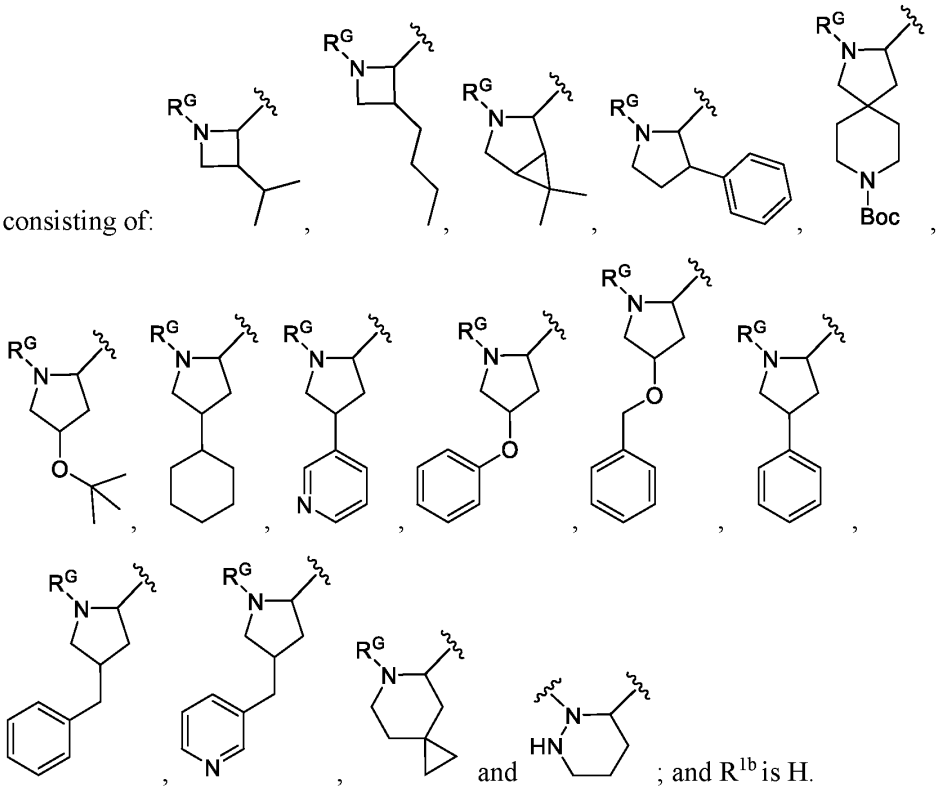
44. R^3 is selected from the group consisting of  ,  ,  ,  ,  , and .

45. R^2 is selected from the group consisting of  ,  ,  ,

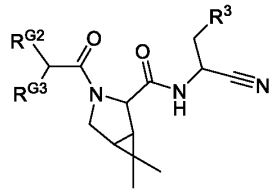




46. R^{1a} and R^2 are joined to together to form the heterocycle selected from the group consisting of:

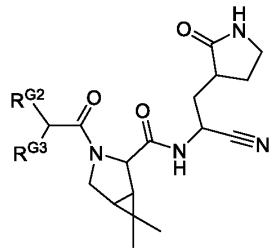


48. The compound is represented by:



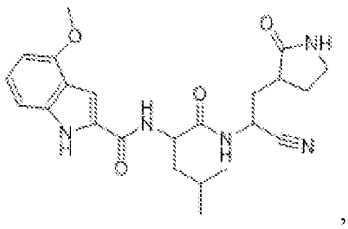
wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, methyl or CF_3.

49. The compound is represented by:

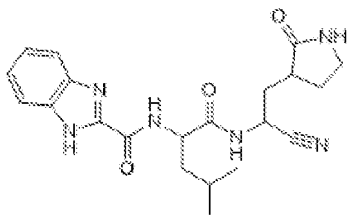


wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, methyl or CF_3.

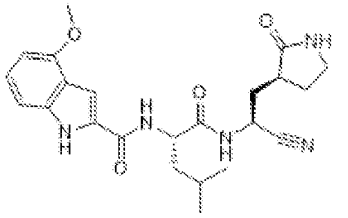
50. The compound is selected from the group consisting of:



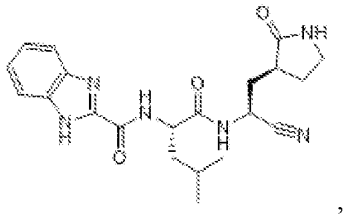
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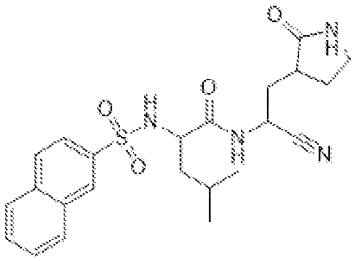
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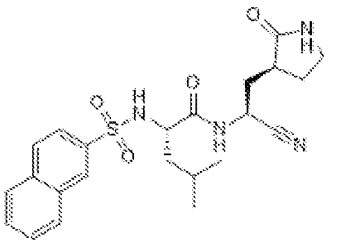
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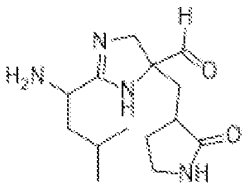
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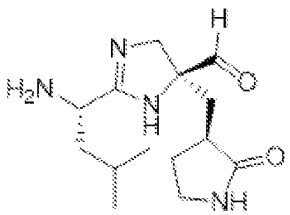
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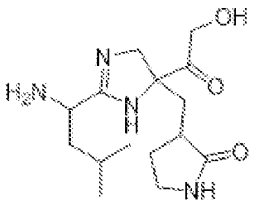
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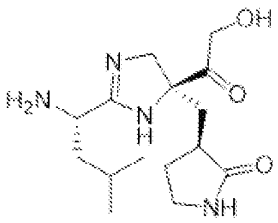
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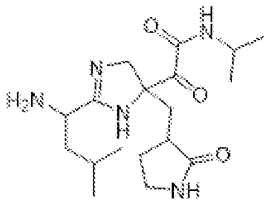
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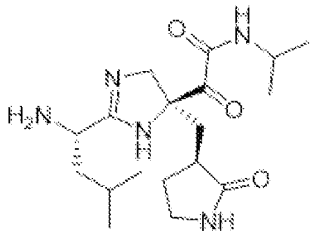
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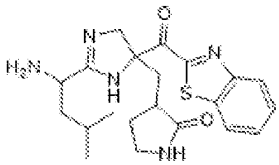
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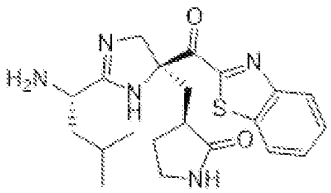
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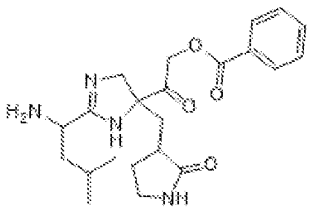
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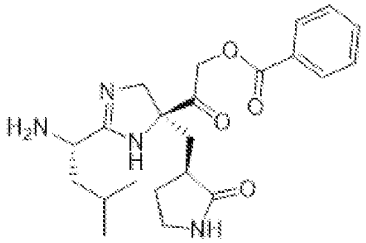
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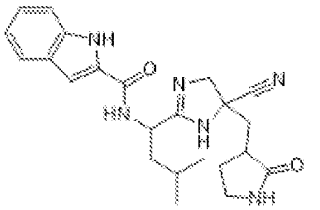
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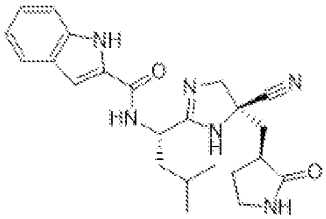


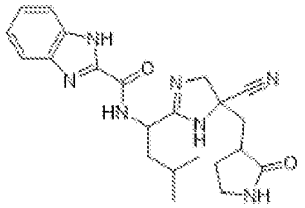
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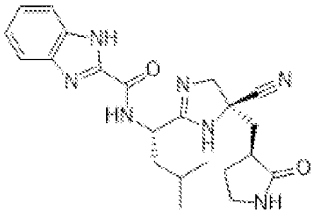


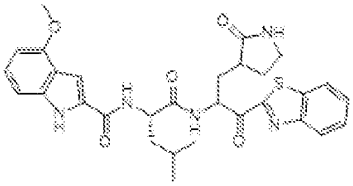
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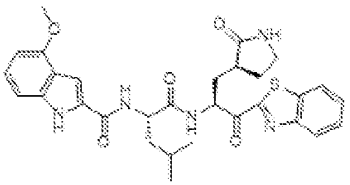

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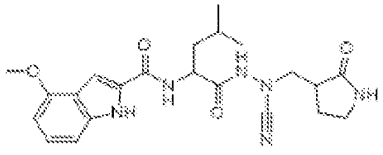

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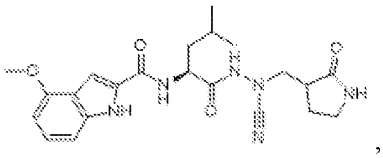

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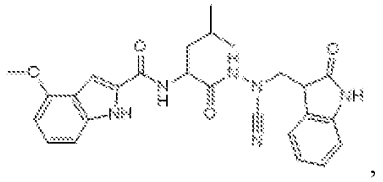

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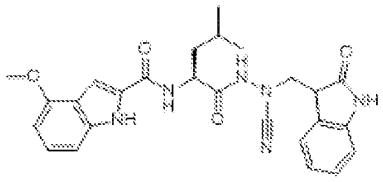

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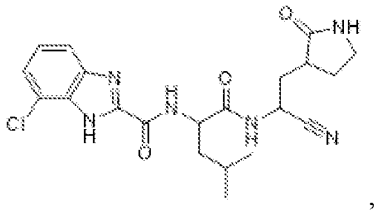

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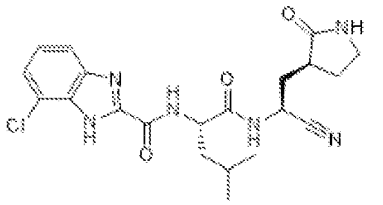

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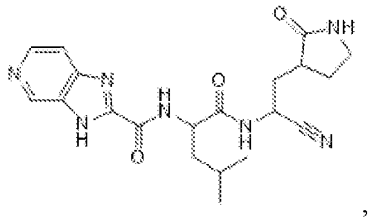

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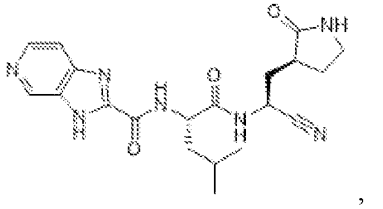

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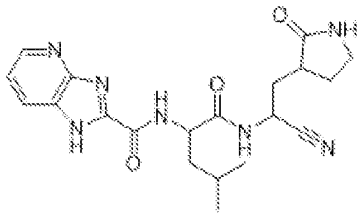

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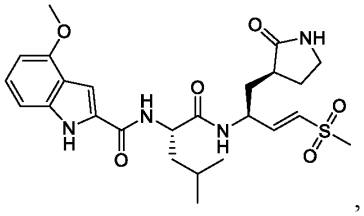

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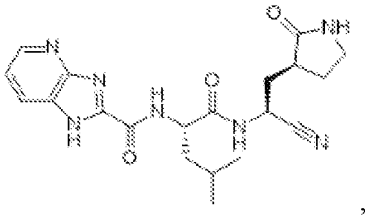

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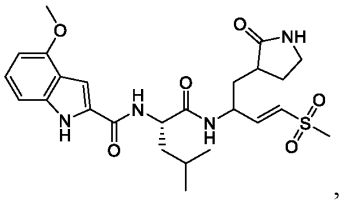
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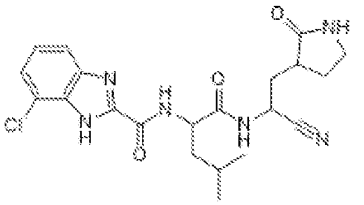
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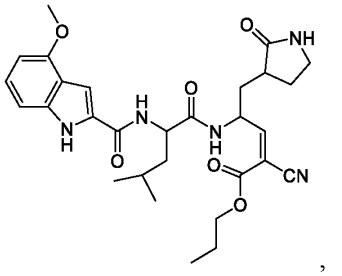
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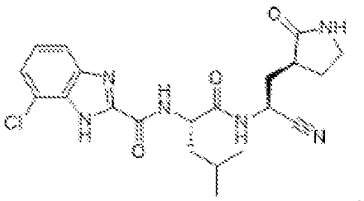
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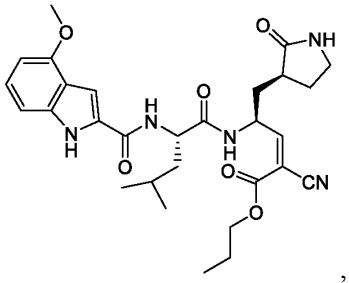
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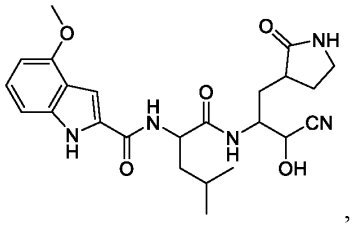
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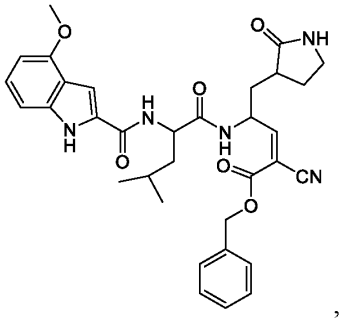
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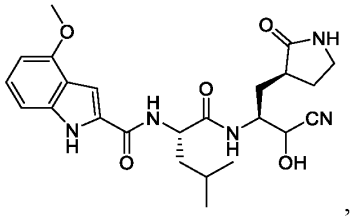
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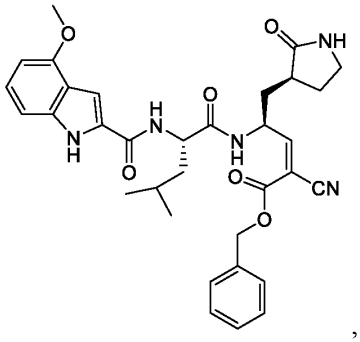
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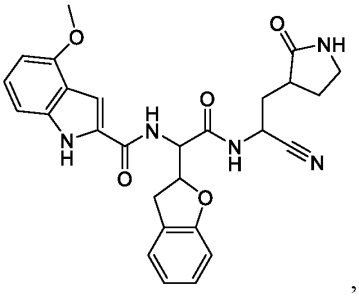
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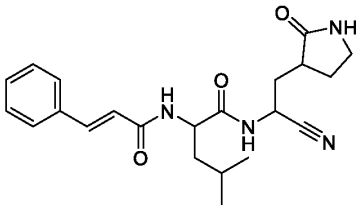
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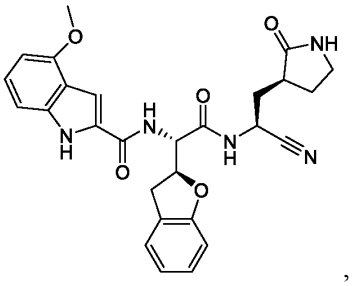
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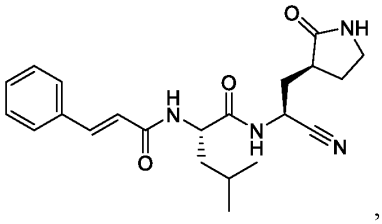
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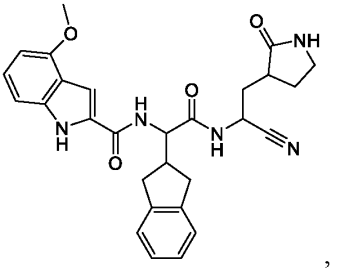
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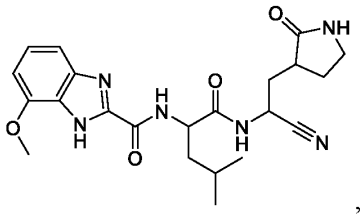
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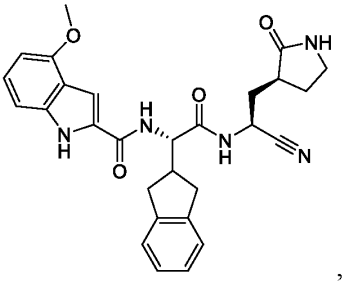
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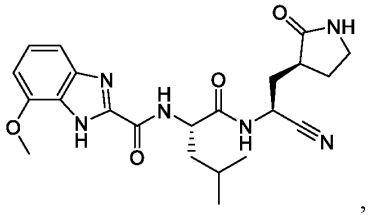
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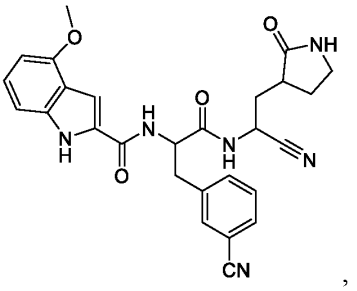
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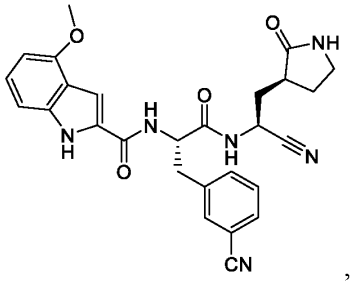
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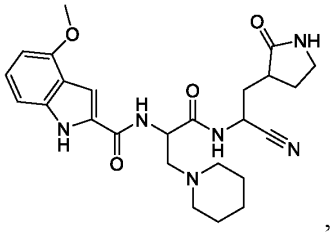
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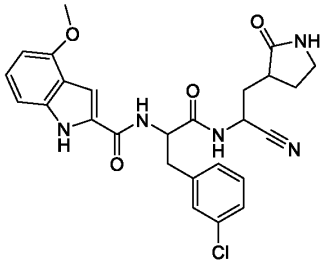
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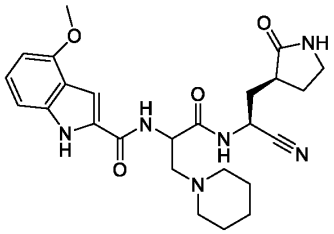
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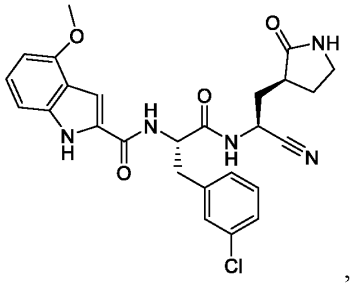
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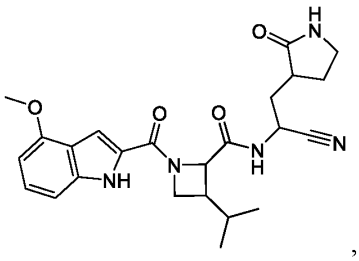
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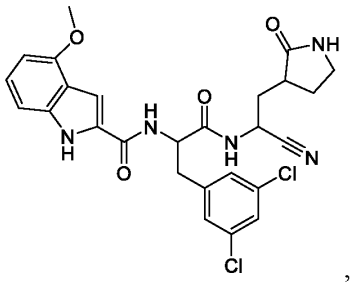
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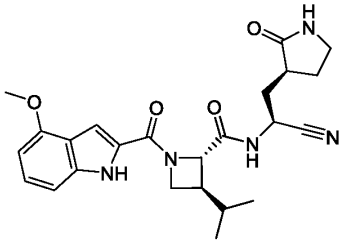
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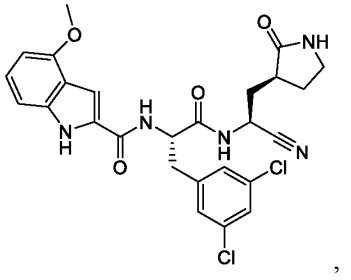
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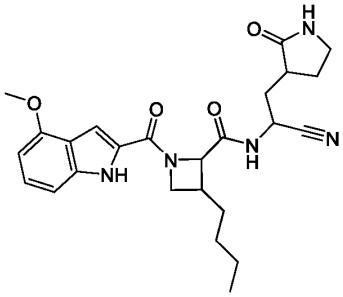
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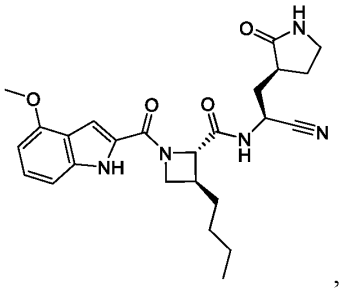
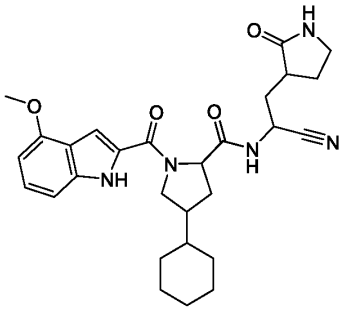
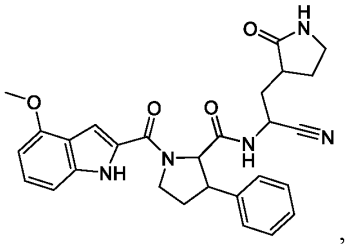
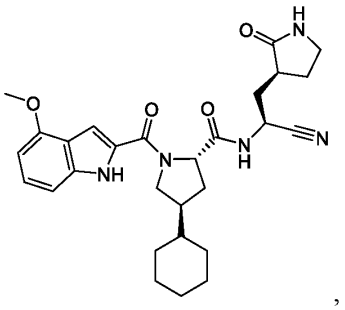
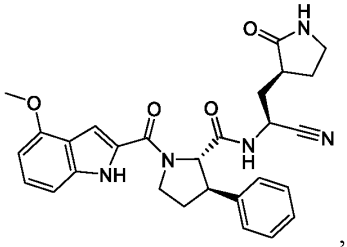
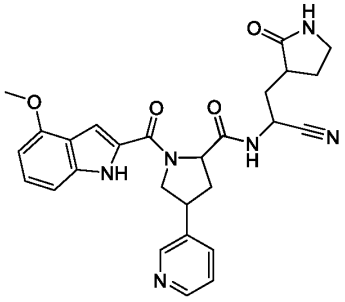
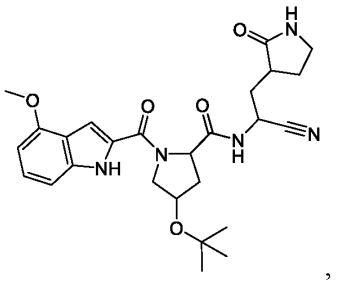
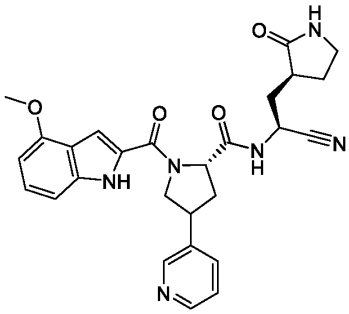
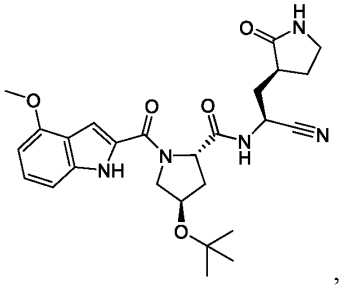
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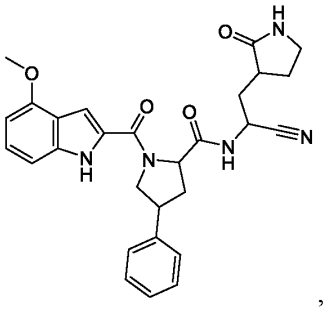


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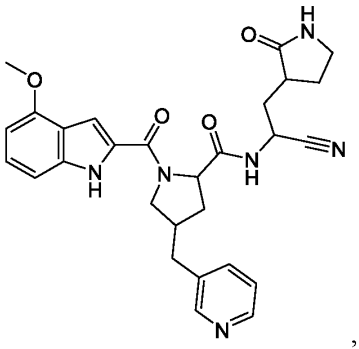


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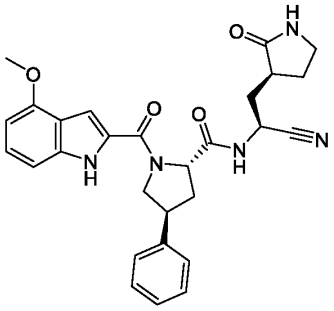

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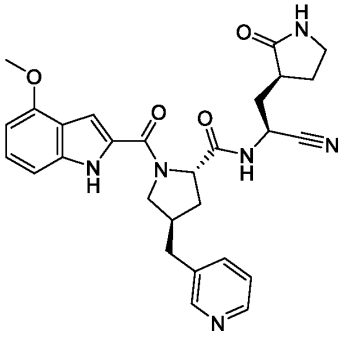
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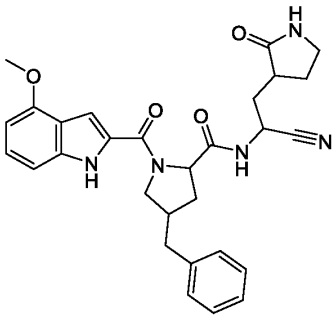
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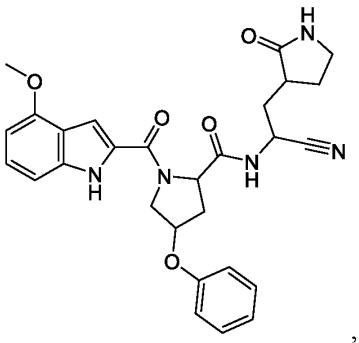
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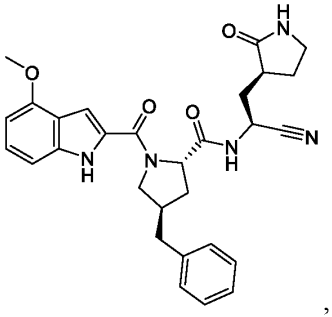
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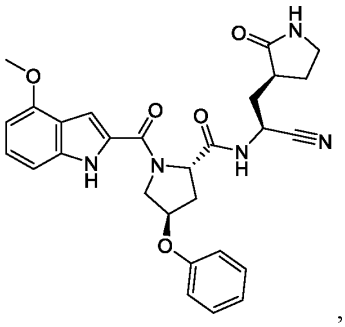
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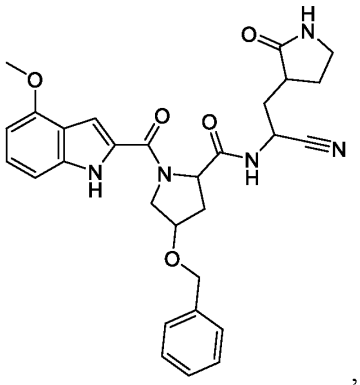
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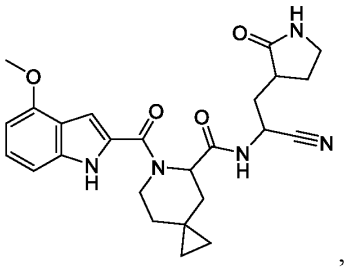
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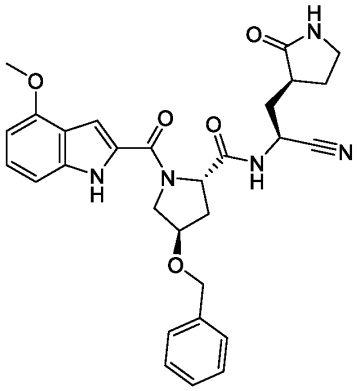
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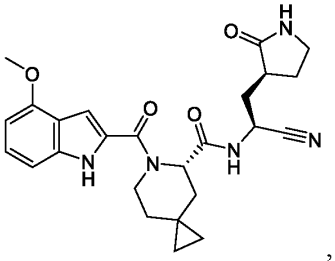
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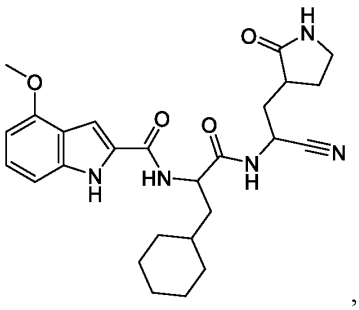
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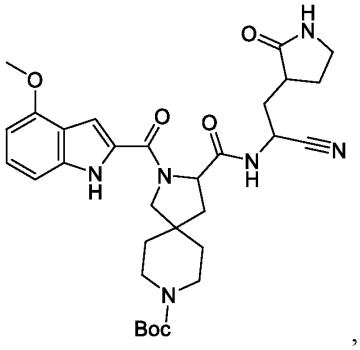
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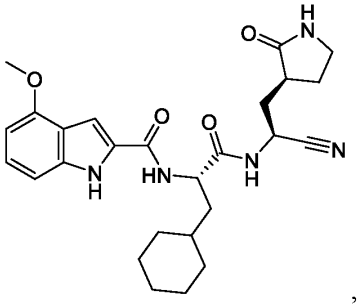
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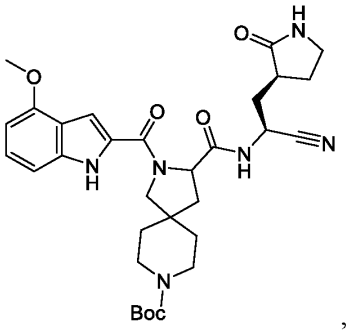
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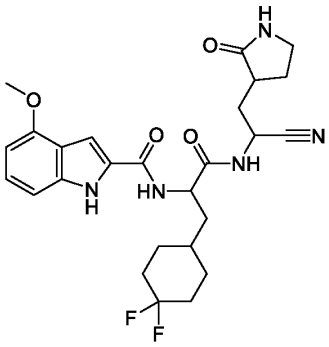
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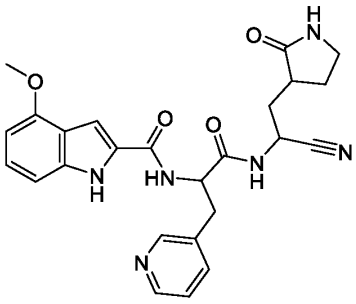


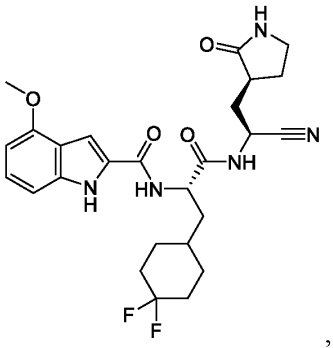
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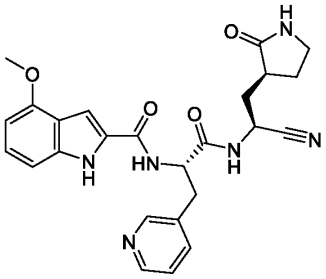


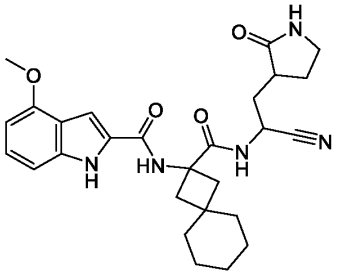
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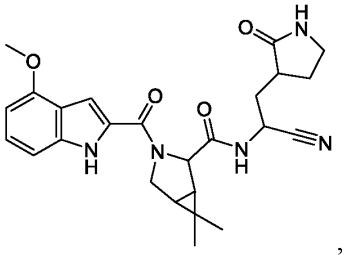

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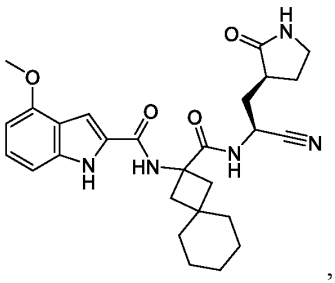

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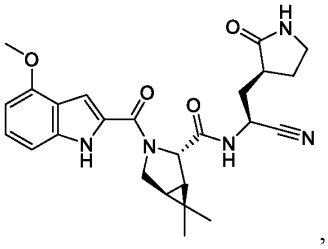

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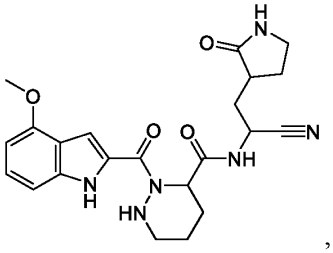

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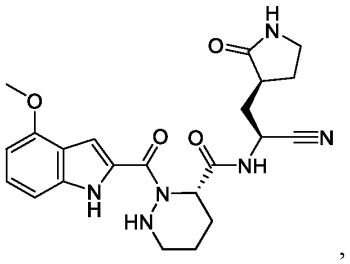
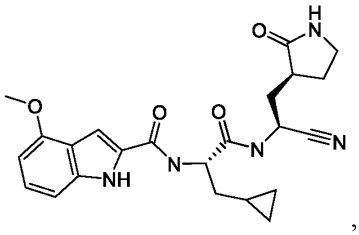
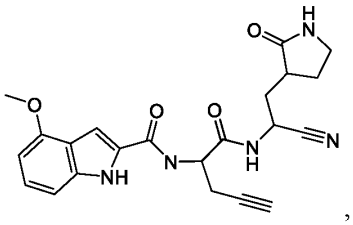
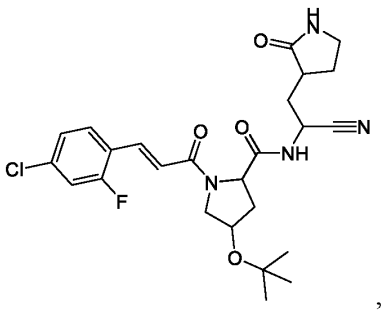
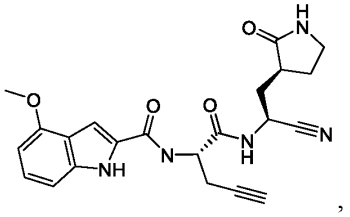
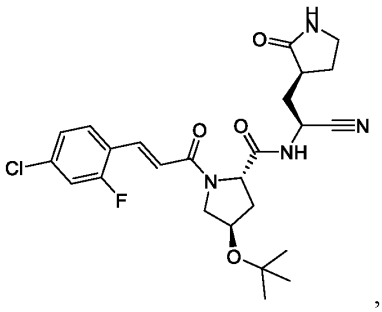
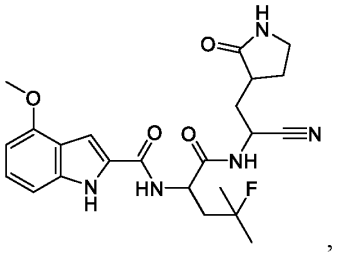
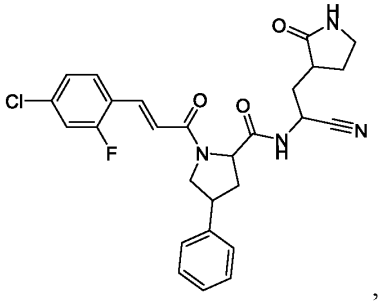
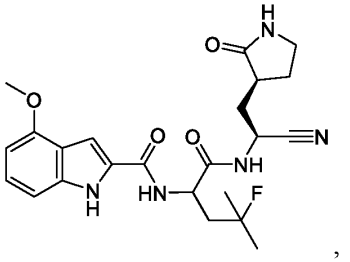
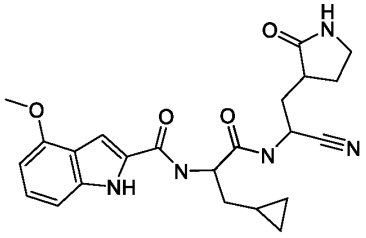

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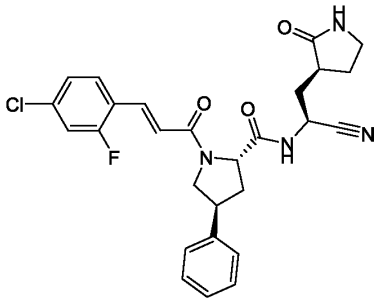
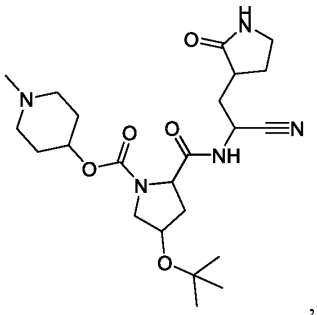
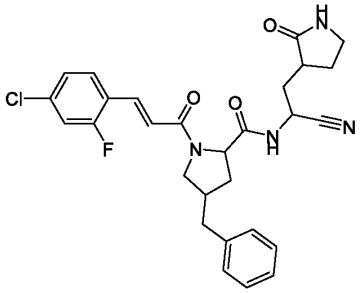
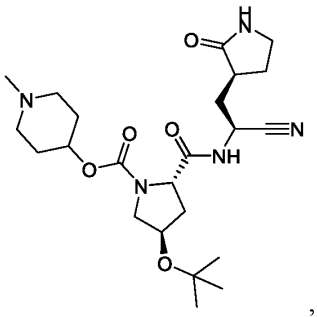
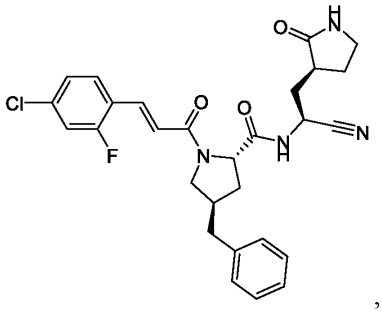
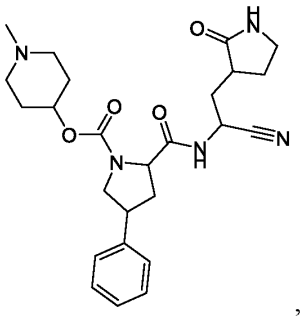
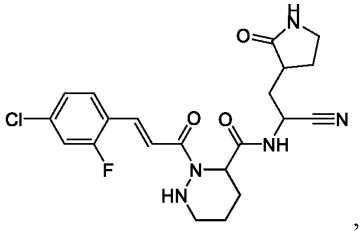
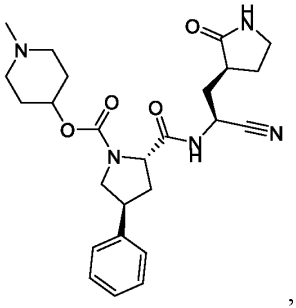
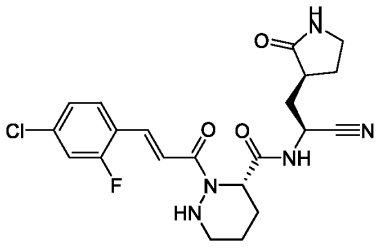

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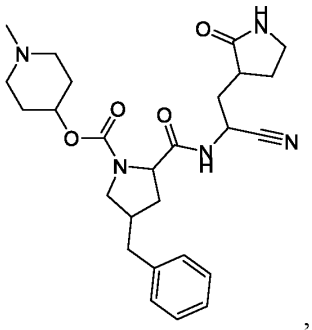

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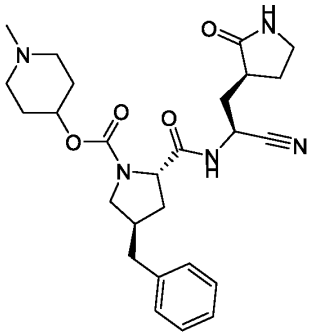

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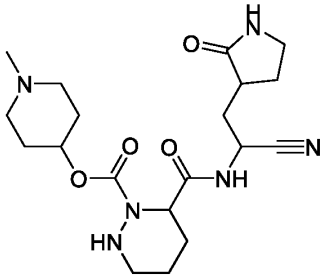

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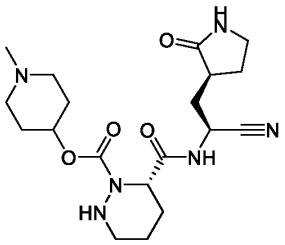
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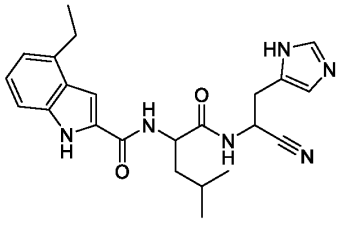
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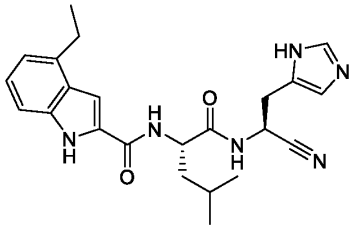
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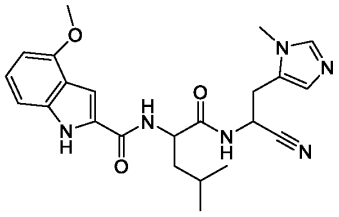
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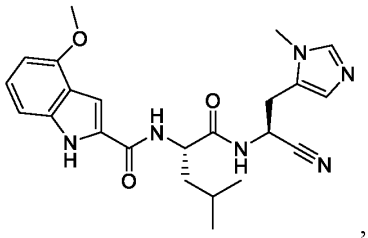
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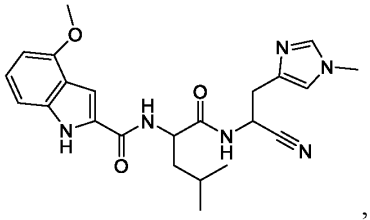
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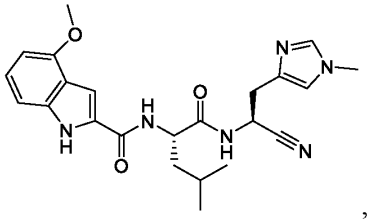
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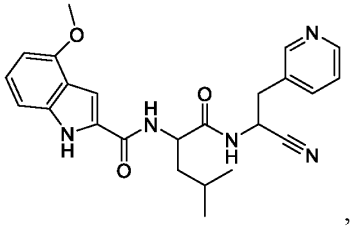
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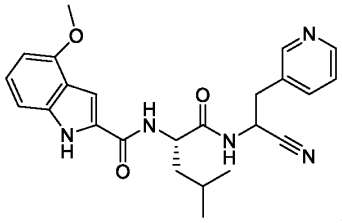
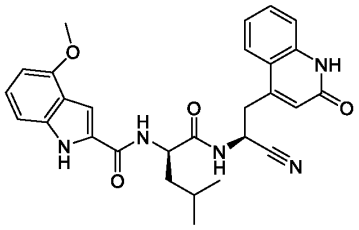
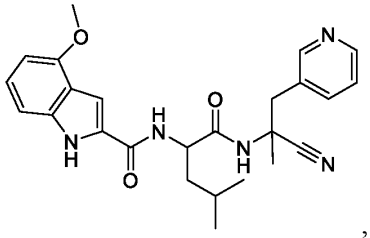
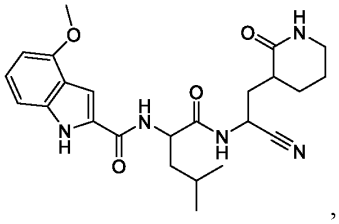
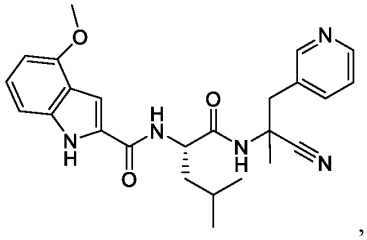
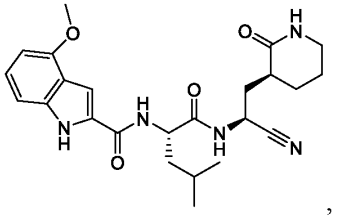
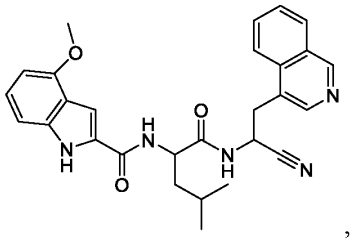
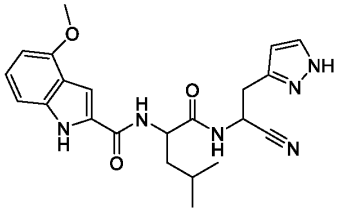
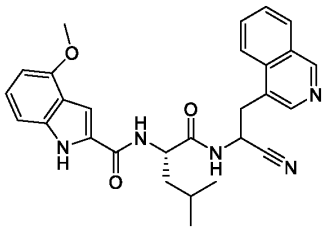
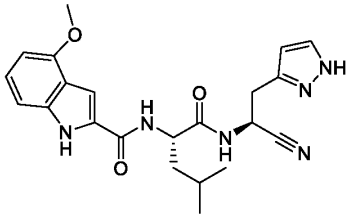
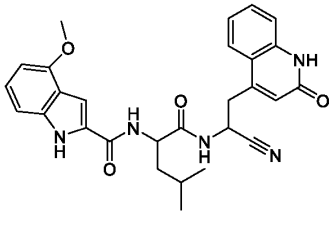
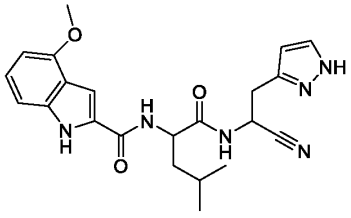
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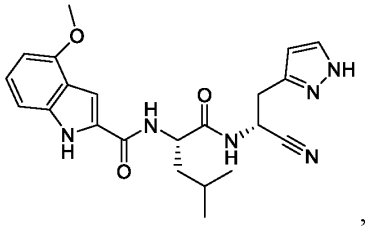
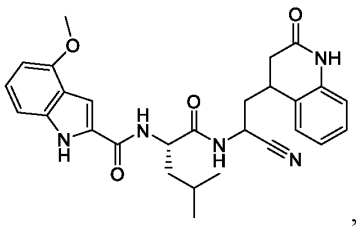
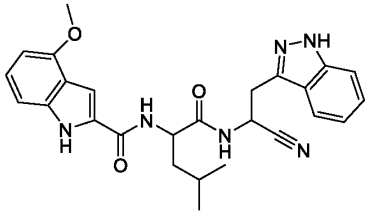
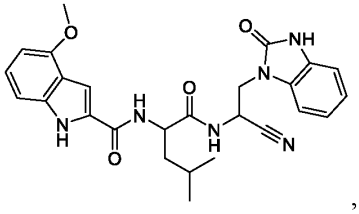
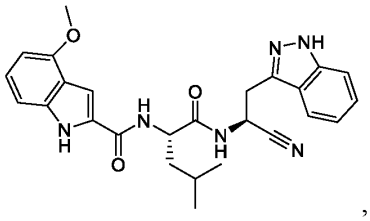
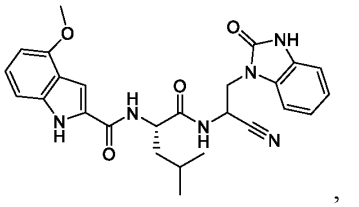
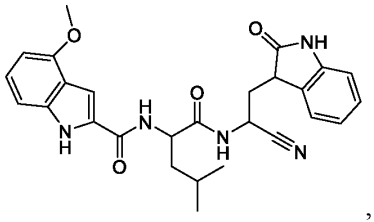
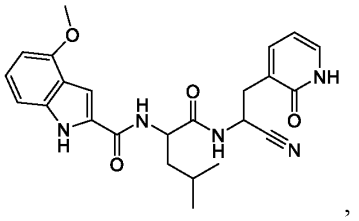
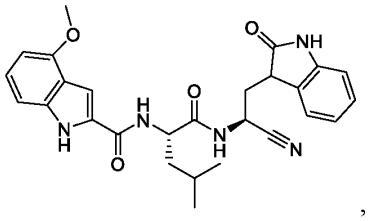
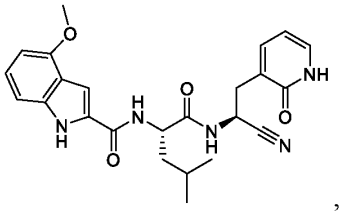
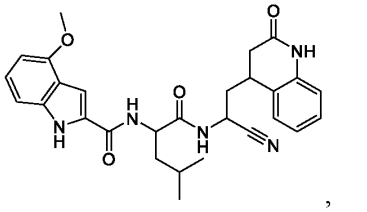
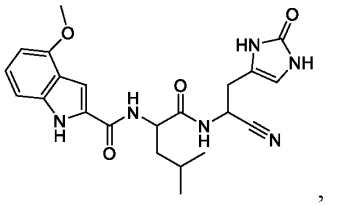


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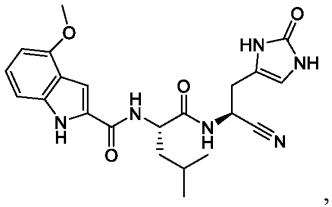
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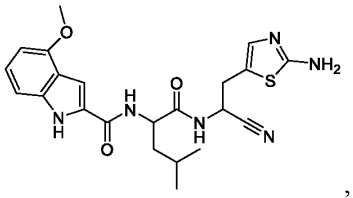

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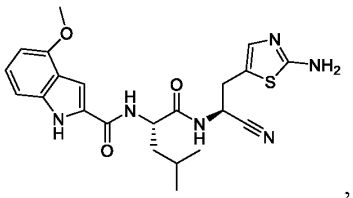
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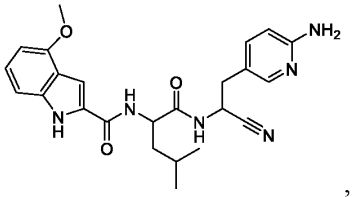
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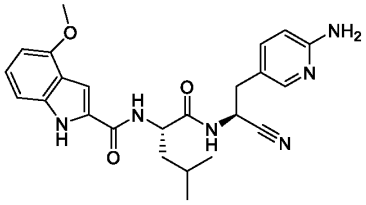
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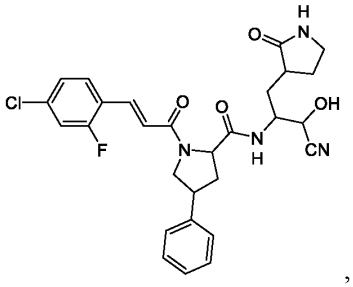
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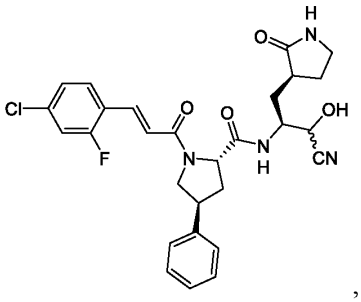
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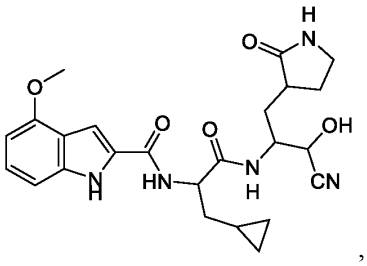
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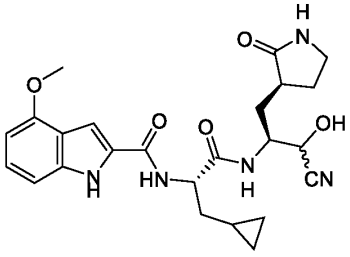
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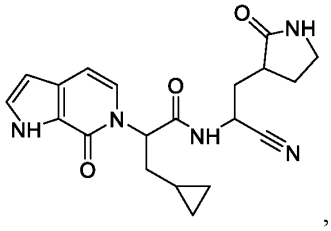
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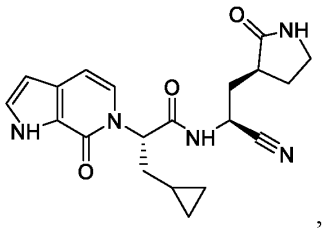
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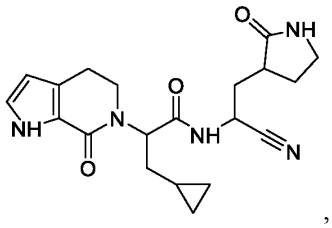
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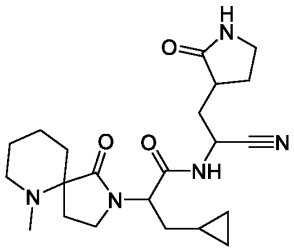


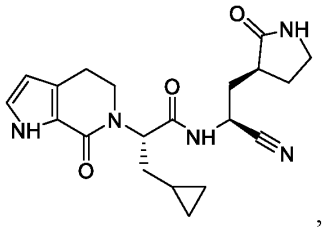
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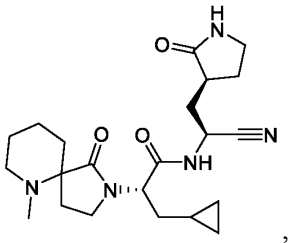


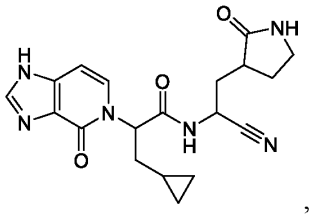
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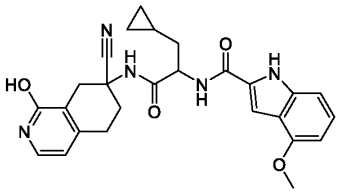

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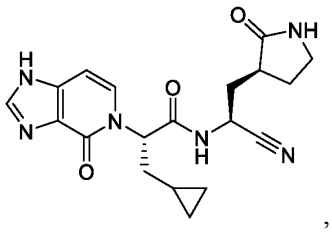

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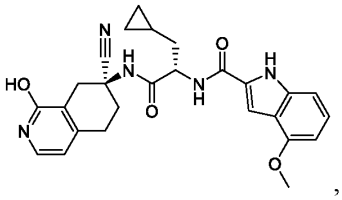

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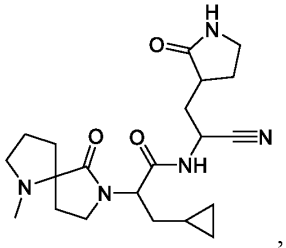

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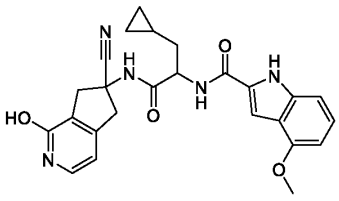

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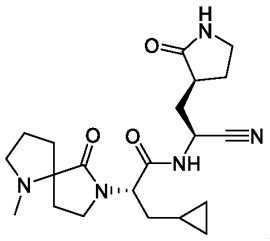

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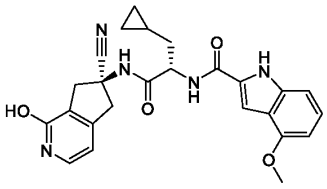

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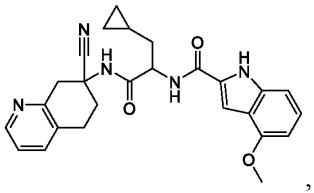

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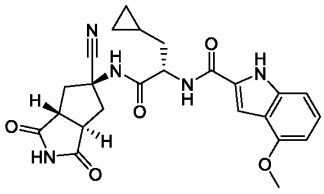

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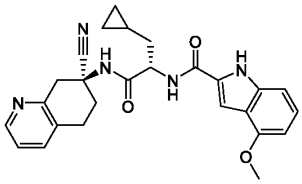

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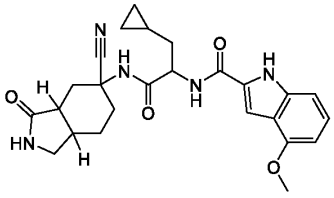

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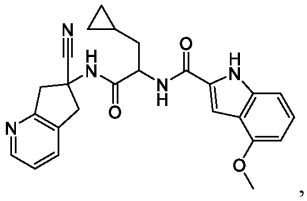

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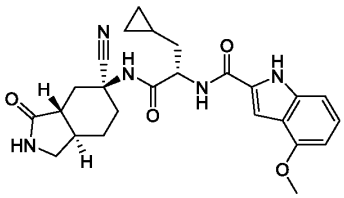

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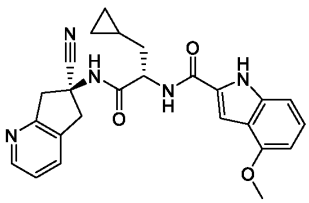

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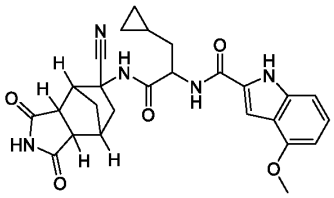

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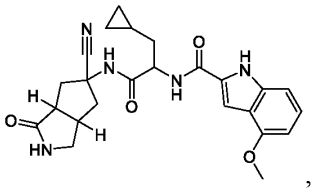

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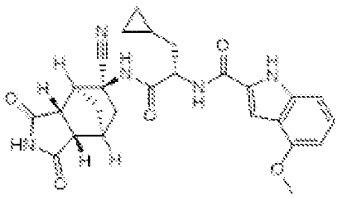

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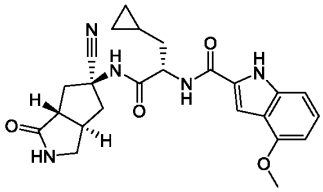

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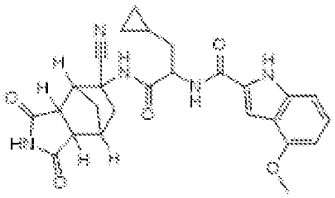

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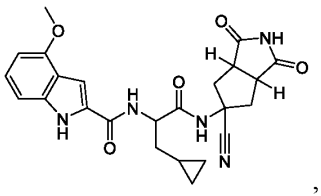

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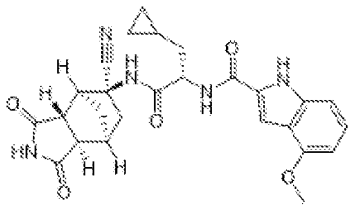

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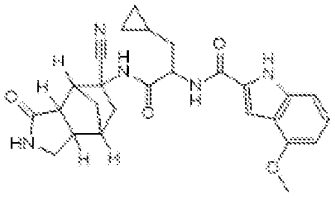

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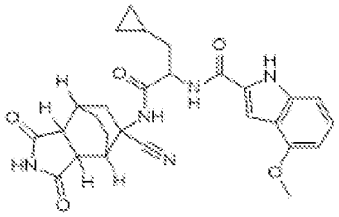

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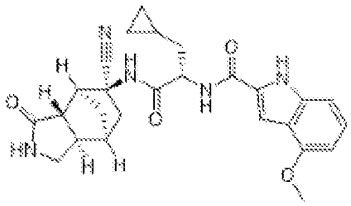

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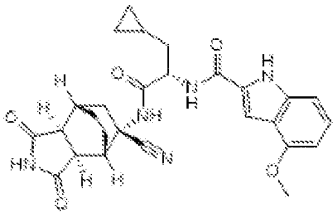
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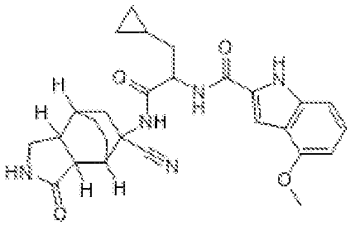
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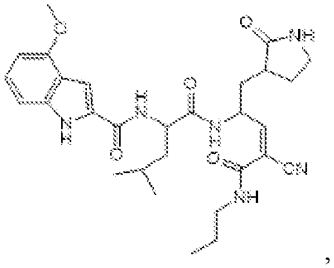
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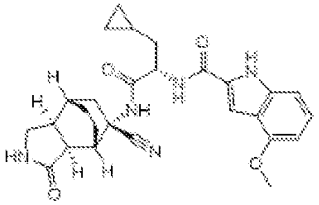
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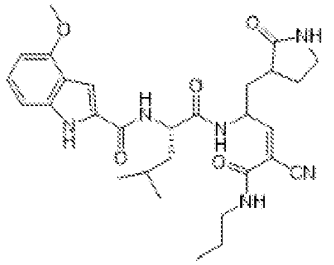
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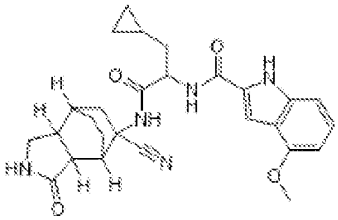
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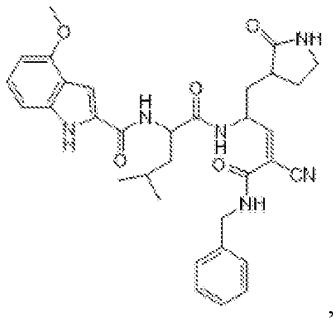
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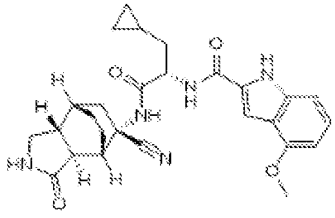
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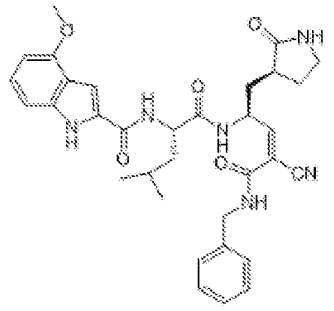
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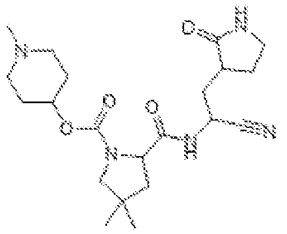
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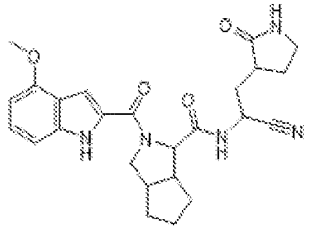
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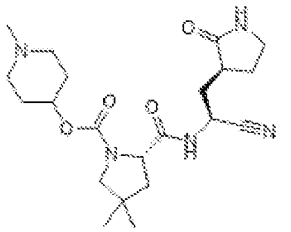
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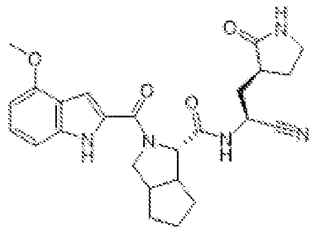
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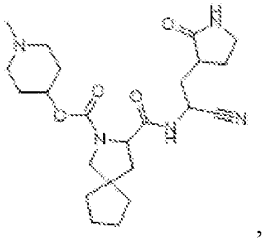
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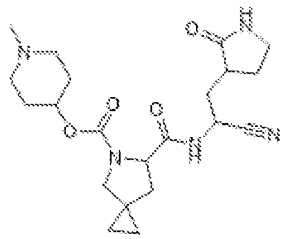
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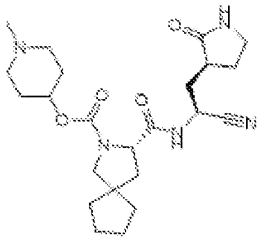
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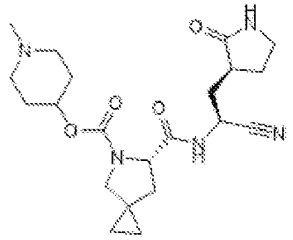
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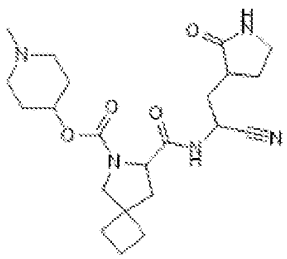
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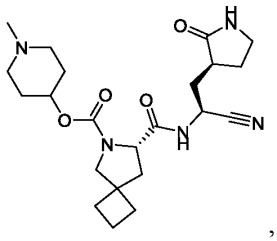
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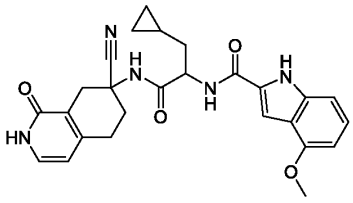
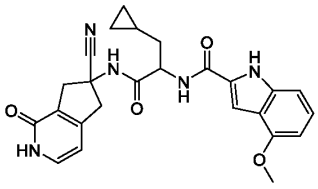
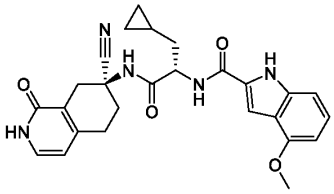
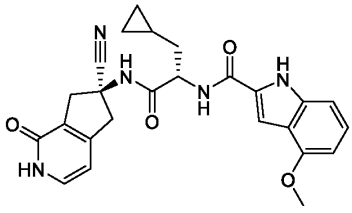
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51. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds of the embodiment

52. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
53. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.
54. The viral infection is a coronavirus infection.
55. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).

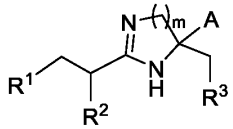
56. The viral infection is SARS-CoV-2.
57. The viral infection is an arenavirus infection.
58. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.
59. The viral infection is an influenza infection.
60. The influenza is influenza H1N1, H3N2 or H5N1.
61. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of any compound the embodiment to a patient suffering from the virus, and/or contacting an effective amount of any compound of the embodiment with a virally infected cell.
62. The method further comprises administering another therapeutic.
63. The method further comprises administering an additional anti-viral therapeutic.
64. The anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, and remdesivir.
65. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.
66. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, and remdesivir.

67. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of any compound of the embodiment.
68. The compound is administered before viral exposure.
69. The compound is administered after viral exposure.

7. Contemplated Embodiment

[000196] In another aspect, the compositions, compounds and methods of the present disclosure may be described in another embodiment as follows:

1. A protease inhibitor compound represented by:



Formula I,

wherein:

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NH_2$, $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10 membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-

C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

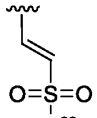
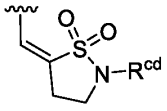
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a warhead;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

m is 1 or 2; and

pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

2. A is selected from the group consisting of cyano, –$C(O)R^D$, –$C(O)CH_2N(R^bR^c)$, –$C(O)CH_2OC(O)R^D$, –$C(O)C(O)R^D$, –$(CH=CH)C(O)OR^D$, –$(CH=CCN)C(O)OR^D$, –$(CH=CCN)C(O)(NH)R^D$, –CH(CN)(OH), -$CH(CN)(NR^bR^c)$,  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} –$N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

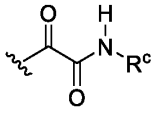
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

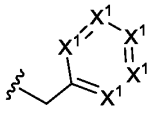
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

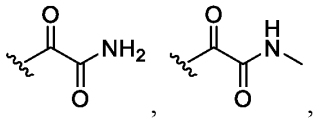
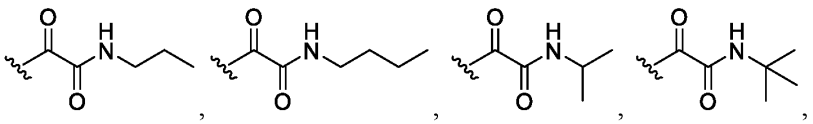
R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

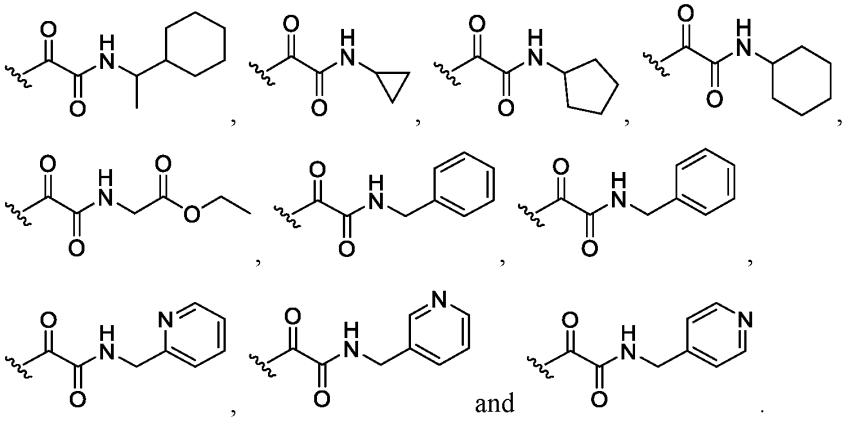
R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

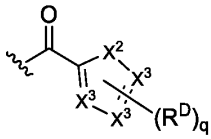
R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

3. A is a warhead represented by:  , wherein R^c is selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), C_1-C_8alkyl, and C_3-C_6cycloalkyl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, 5-10 membered aryl and 5-10 membered heteroaryl.

4. R^c is  , wherein X^1 is independently selected, for each occurrence, from N and CH.

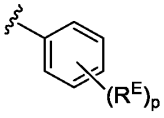
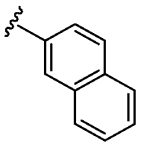
5. A is selected from the group consisting of  , 



6. A is  , wherein

X^2 is selected from the group consisting of NH, O and S;

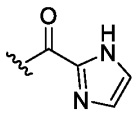
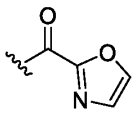
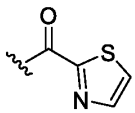
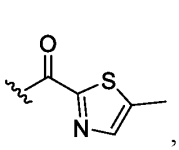
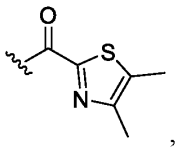
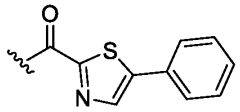
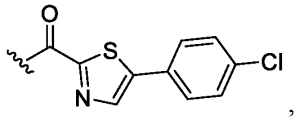
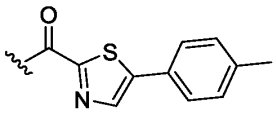
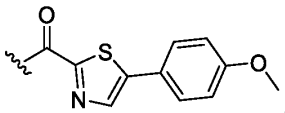
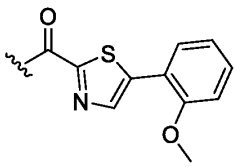
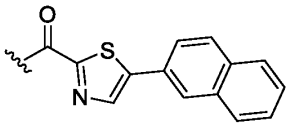
X^3 is independently selected, for each occurrence, from N and CH;

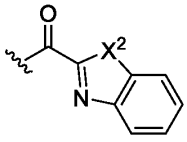
R^D is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl,  and  ;

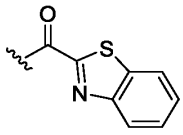
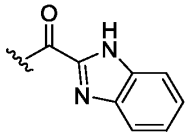
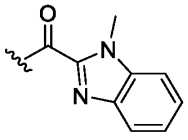
R^E is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, C_1-C_8alkyl and C_1-C_8alkoxy;

p is selected from 0, 1 and 2; and

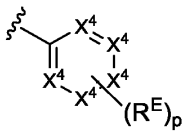
q is selected from 0, 1 and 2.

7. A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

8. A is  , wherein X^2 is selected from the group consisting of NH, NR^P, O and S, wherein R^P is C_1-C_8alkyl.

9. A is selected from the group consisting of  ,  and  .

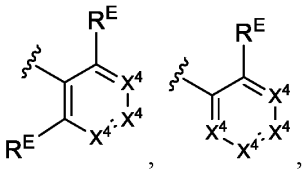
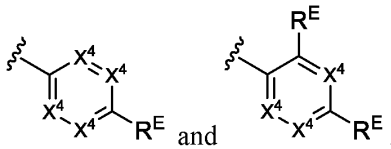
10. A is–$C(O)CH_2OC(O)R^D$, wherein

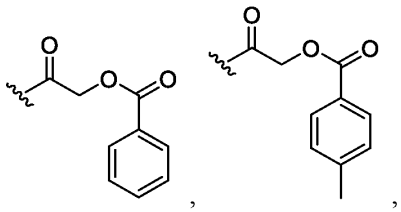
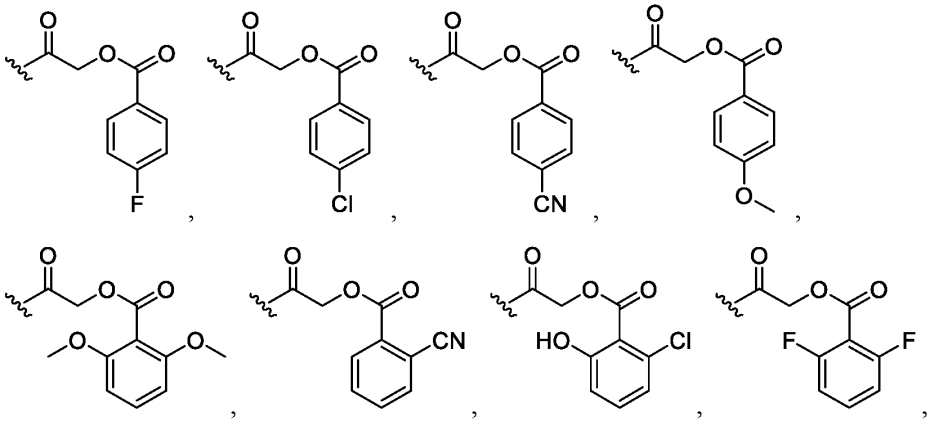
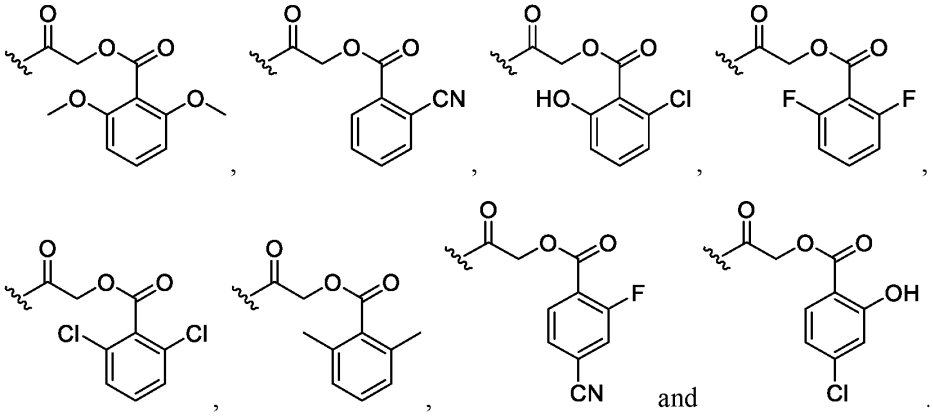
R^D is selected from the group consisting of  , C_1-C_8alkyl and C_3-C_6cycloalkyl;

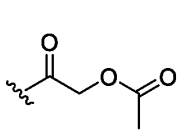
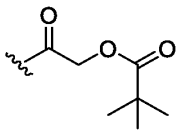
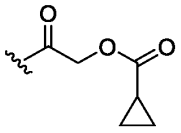
X^4 is independently selected, for each occurrence, from CH and N;

R^E is independently selected, for each occurrence, from the group consisting of halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-CF_3$, $-OCF_3$ and $-SCF_3$; and

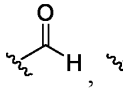
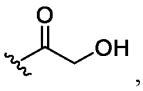
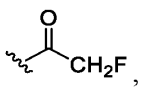
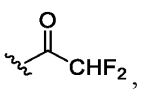
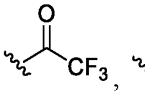
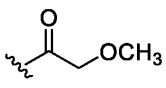
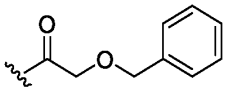
p is selected from 0, 1 and 2.

11. R^D is selected from the group consisting of  ,  and .

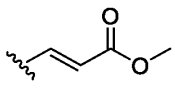
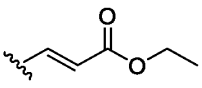
12. A is selected from the group consisting of  ,  ,  and .

13. A is selected from the group consisting of  ,  and  .

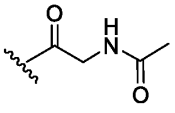
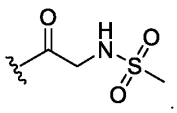
14. A is–C(O)R^D, wherein R^D is selected from the group consisting of hydrogen, –CH_2OH, -CH_2OR' and –CH_xF_y, wherein R' is selected from the group consisting of C_1-C_8alkyl, -(C_1-C_8alkyl)-(5-10 membered aryl), C_1-C_8heteroalkyl, C_3-C_6cycloalkyl and 5-10 membered aryl, wherein x is 0, 1 or 2; y is 1, 2 or 3; and the sum of x and y is 3.

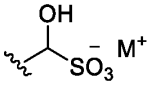
15. A is selected from the group consisting of  ,  ,  ,  ,  ,  and  .

16. A is –(CH=CH)C(O)OR^D, wherein R^D is C_1-C_8alkyl.

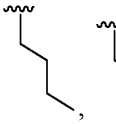
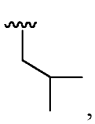
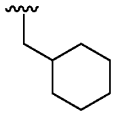
17. A is selected from  and  .

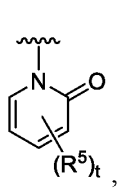
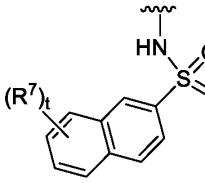
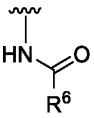
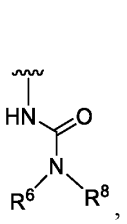
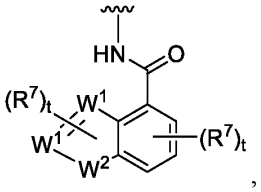
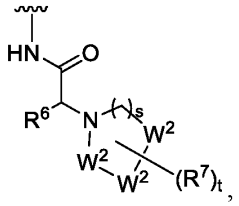
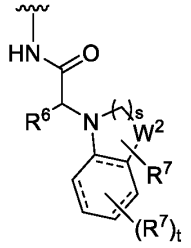
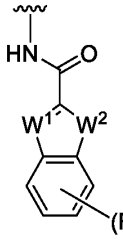
18. A is–C(O)$CH_2N(R^bR^c)$.

19. A is a warhead selected from  and  .

20. A is  , wherein M is selected from Na and K.

21. A is cyano.

22. R^1 is selected from the group consisting of  ,  ,  and  .

23. R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and , wherein

======= denotes a bond that may be a single or double bond;

R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^6 is C_1-C_8alkyl;

R^7 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

R^8 is selected from the group consisting of 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

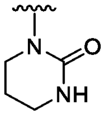
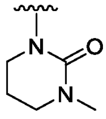
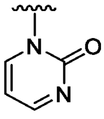
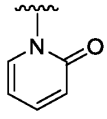
W^1 is selected from CH and N;

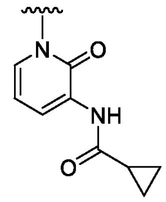
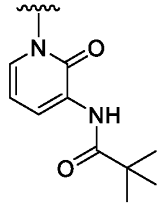
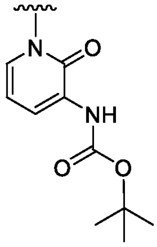
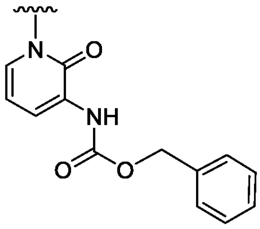
W^2 is selected from the group consisting of CH_2, O, NH and S;

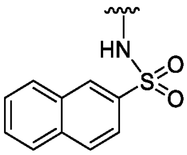
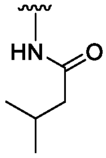
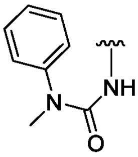
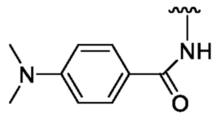
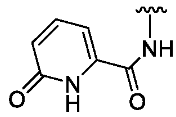
W is selected from W^1 and W^2;

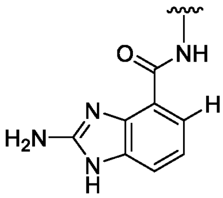
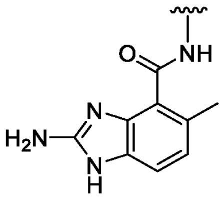
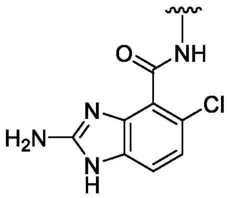
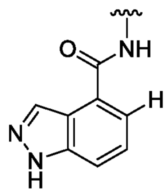
s is selected from 1 and 2; and

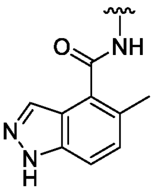
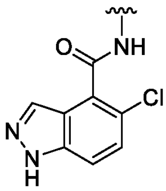
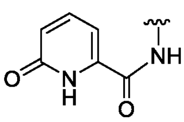
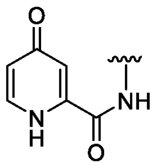
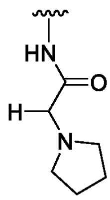
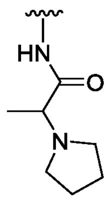
t is selected from 0, 1, 2 and 3.

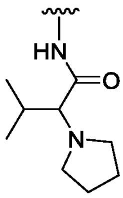
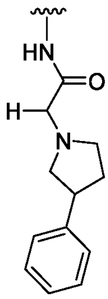
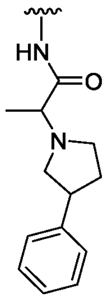
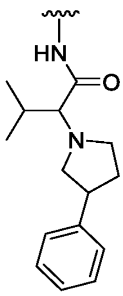
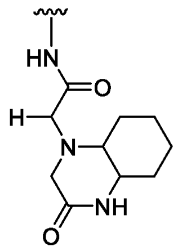
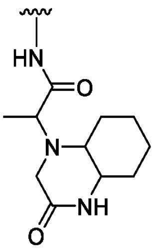
24. R^2 is selected from the group consisting of  ,  ,  ,  ,

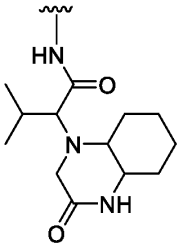
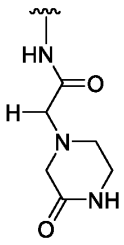
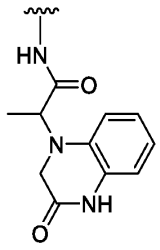
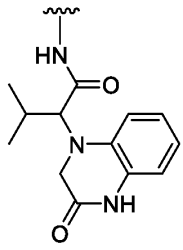
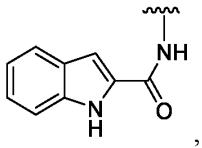
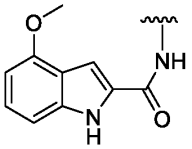
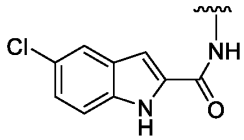
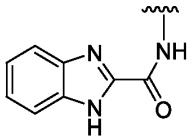
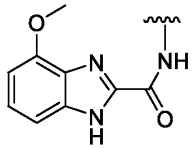
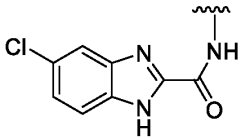
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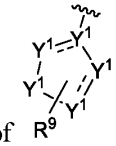
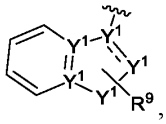
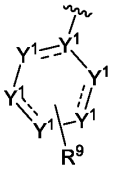
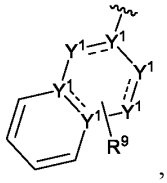
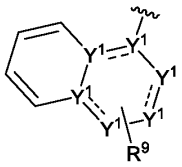
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and


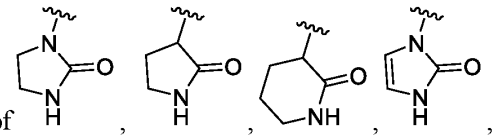
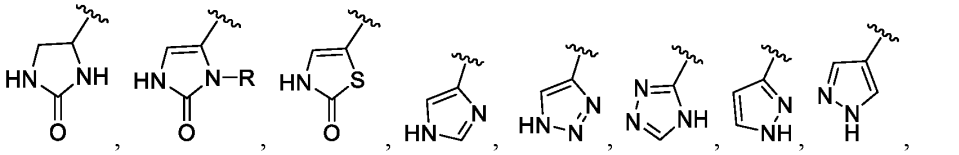
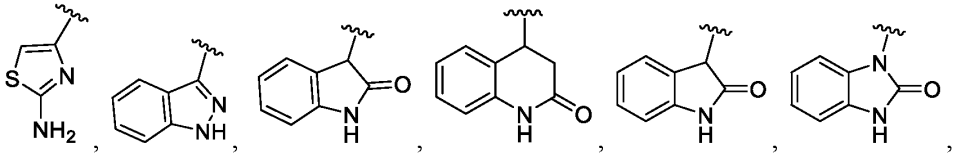
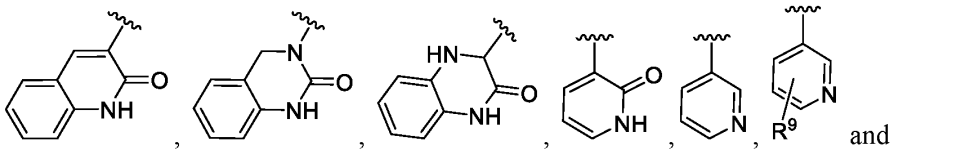
25. R^3 is selected from the group consisting of






wherein

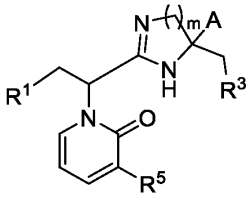
======= denotes a bond that may be a single or double bond;

Y^1 is selected from the group consisting of CH, CH_2, N, NH, O and S;

R^9 is selected from the group consisting of halogen, hydroxyl, oxo, $–NH_2$, $–N(CH_3)_2$, $–N(CH_2CH_3)_2$, $–CH_3$, $–CH_2CH_3$, $–OCH_3$ and $–OCH_2CH_3$.

26. R^3 is selected from the group consisting of  ,  ,  ,  ,  , and .

27. The compound is represented by



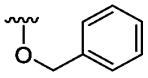
Formula I-A,

wherein:

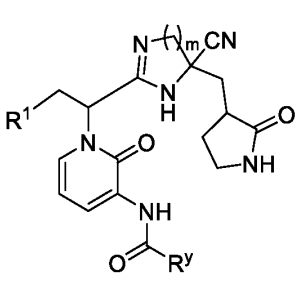
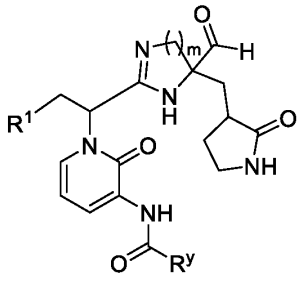
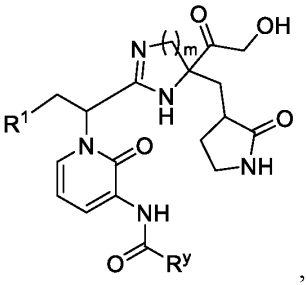
R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

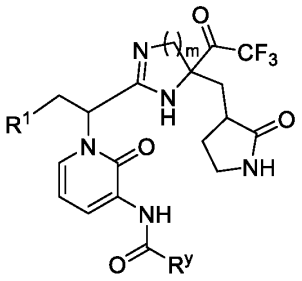
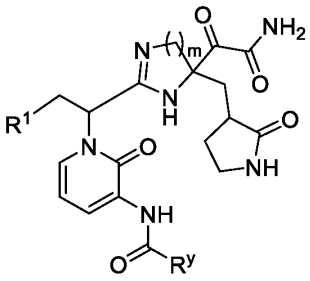
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl; and

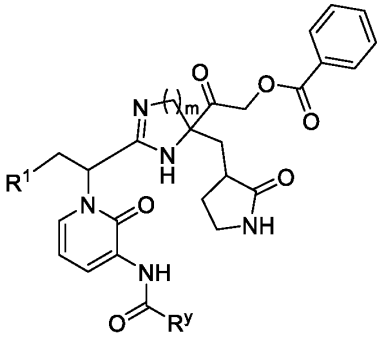
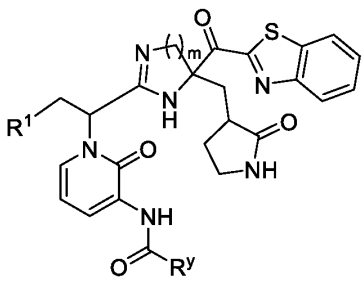
m is selected from 1 and 2.

28. R^y is selected from the group consisting of hydrogen,  ,  ,  and  .

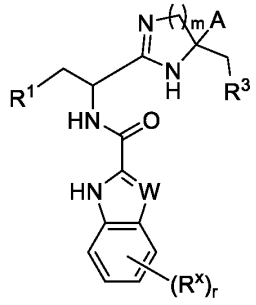
29. The compound is selected from the group consisting of:

 ,  ,  ,

 ,  ,

 , and  .

30. The compound is represented by



Formula I-B,

wherein

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

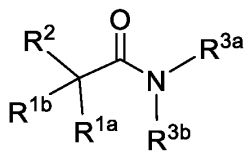
W is CH or N;

m is selected from 1 and 2; and

r is selected from 0, 1, 2 and 3.

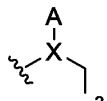
31. R^x is $-OCH_3$.

32. A protease inhibitor compound represented by:



Formula II,

wherein

R^{3a} is selected from  and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of C_1-C_8alkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl; or

R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–NH_2$, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocycle), –C(O)-O-(4-10 membered heterocycle), $–C(O)-OC(CH_3)_3$, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the alkyl, cycloalkyl, heterocycle, heteroaryl, or aryl may optionally be substituted by one, two or three substituents of halogen, C_1-C_6alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl or oxo;

R^2 is selected from the group consisting of –NHC(O)R^B, –NHC(O)N(R^B)$_2$, –NHC(O)C(R^C)$_2$$R^B$, –NHS(O)$_2$$R^B$, 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x; or

R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered mono or bicyclic heterocycle having a ring nitrogen, NR^G, or C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^G is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m) and C(=O)-C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocycle, C_1-C_6alkoxy, wherein R^m is selected for each occurrence by H, C_{1-3}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, optionally substituted phenyl, -S(O)$_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl), C(=O)-C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), C(=O)-C_{3-6}cycloalkyl, or

C(=O)-(5-6 membered heteroaryl) (optionally substituted by halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, and C_{1-6}haloalkyl));

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, SF_5, cyano, –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

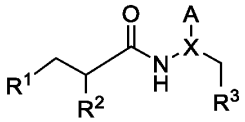
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a warhead;

X is selected from CH, C(CH_3) and N; and

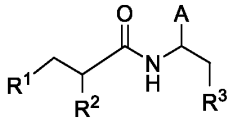
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

33. The compound is represented by:



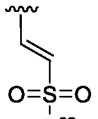
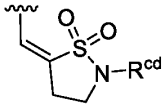
Formula II-A.

34. The compound is represented by:



Formula II-B.

35. A is selected from the group consisting of cyano, –C(O)R^D, –C(O)CH_2N($R^b$$R^c$), –C(O)$CH_2$OC(O)$R^D$, –C(O)C(O)$R^D$, –(CH=CH)C(O)O$R^D$, –(CH=CCN)C(O)O$R^D$, –

(CH=CCN)C(O)(NH)R^D, –CH(CN)(OH), -CH(CN)(NR^bR^c),  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} – $N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

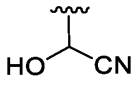
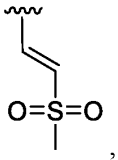
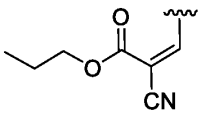
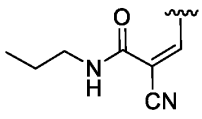
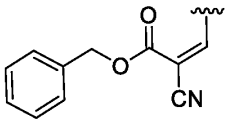
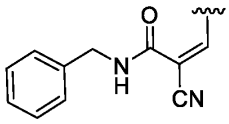
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

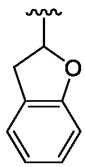
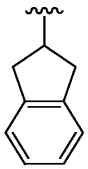
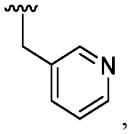
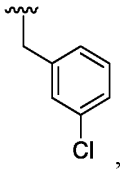
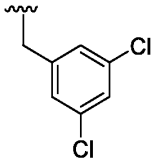
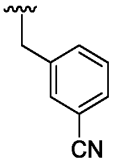
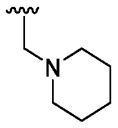
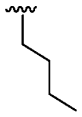
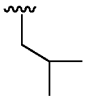
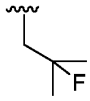
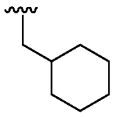
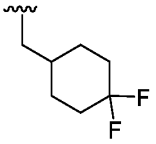
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

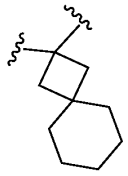
R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

36. A is selected from the group consisting of -CN,  ,  ,  ,  ,  , and  .

37. R^{1a} is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

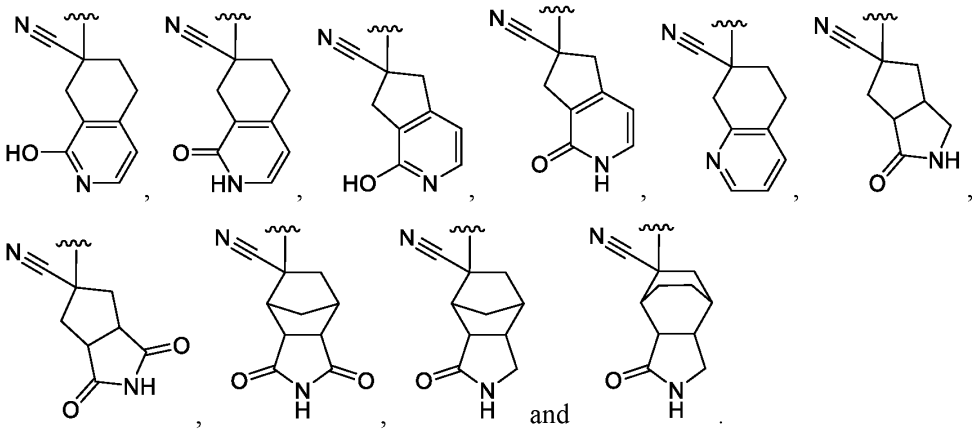
38. R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

39. R^{1b} is hydrogen.

40. R^{1a} and R^{1b} are joined to together to form  .

41. R^{3a} is a 4-10 membered heterocycle substituted by A.

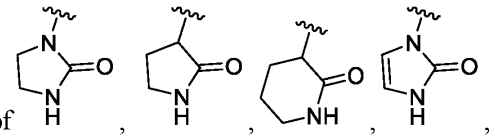
42. R^{3a} is selected from the group consisting of

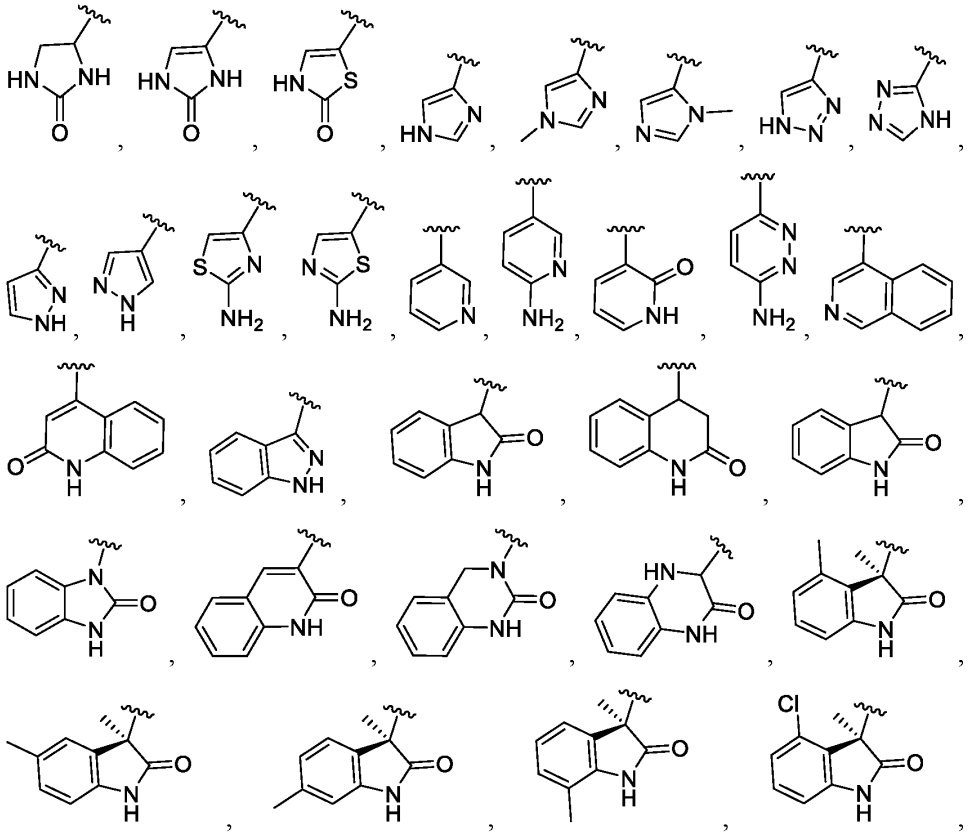


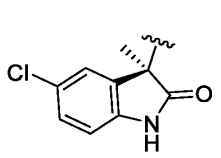
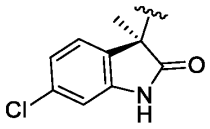
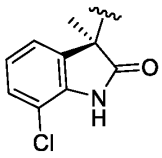
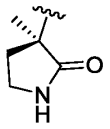
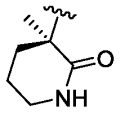
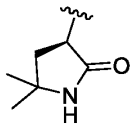
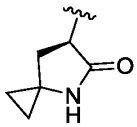
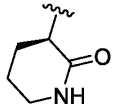
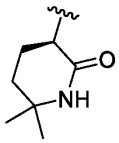
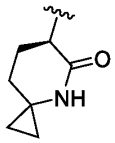
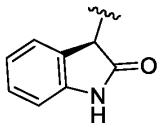
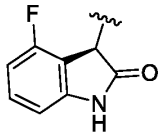
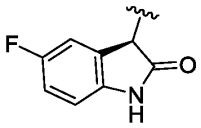
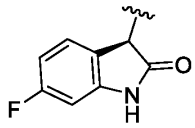
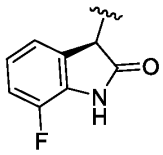
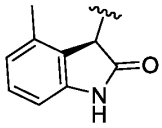
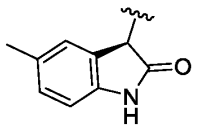
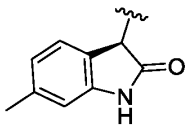
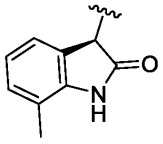
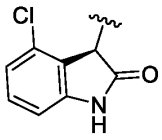
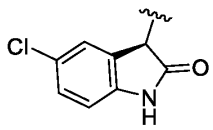
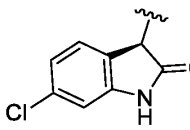
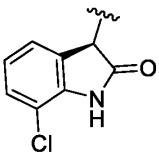
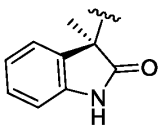
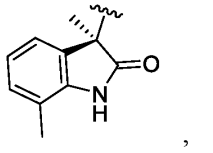
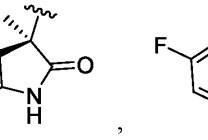
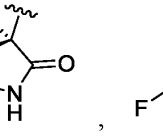
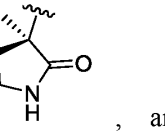
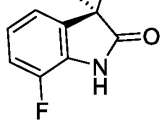
and .

43. R^3 is a 4-10 membered heterocycle.

44. R^3 is selected from the group consisting of





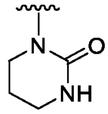
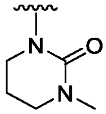
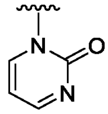
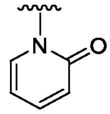

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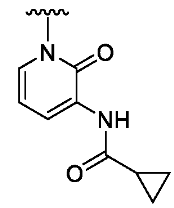
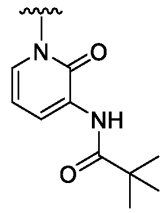
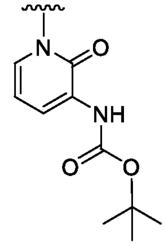
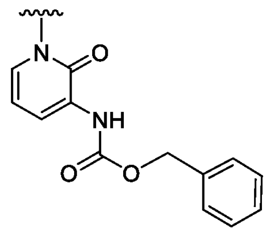
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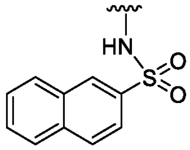
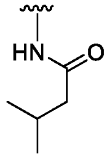
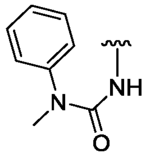
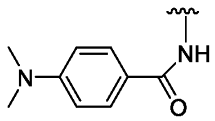
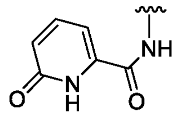
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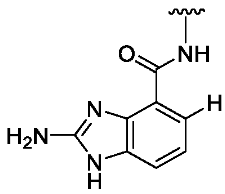
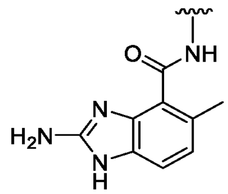
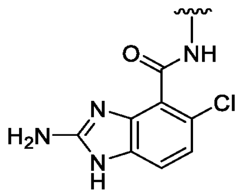
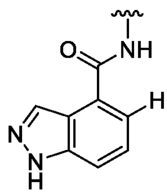
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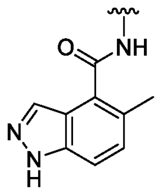
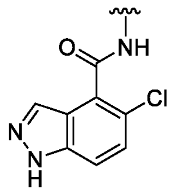
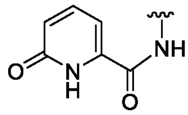
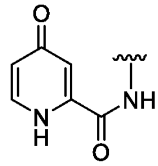
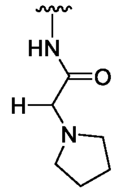
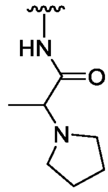
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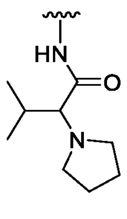
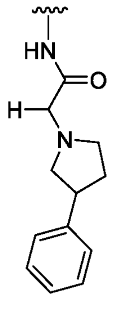
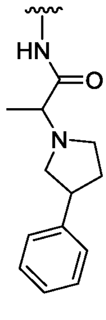
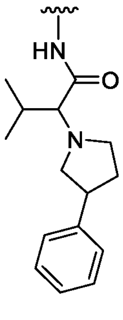
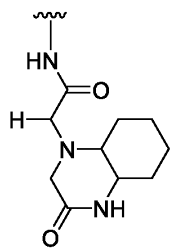
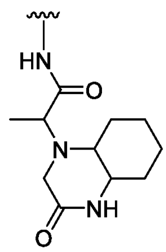
45. R^2 is selected from the group consisting of  ,  ,  ,  ,

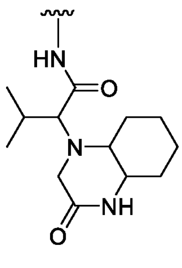
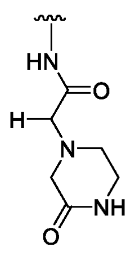
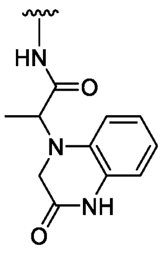
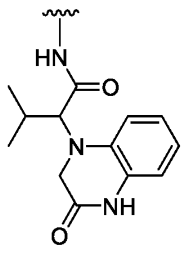
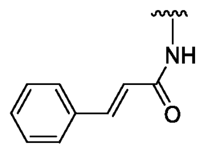
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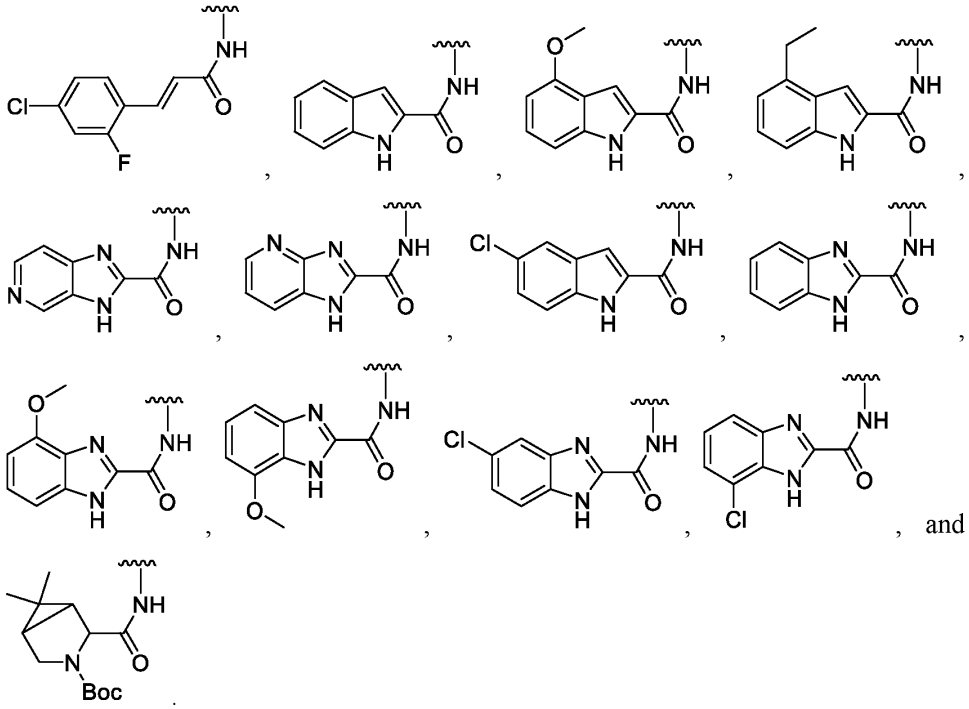
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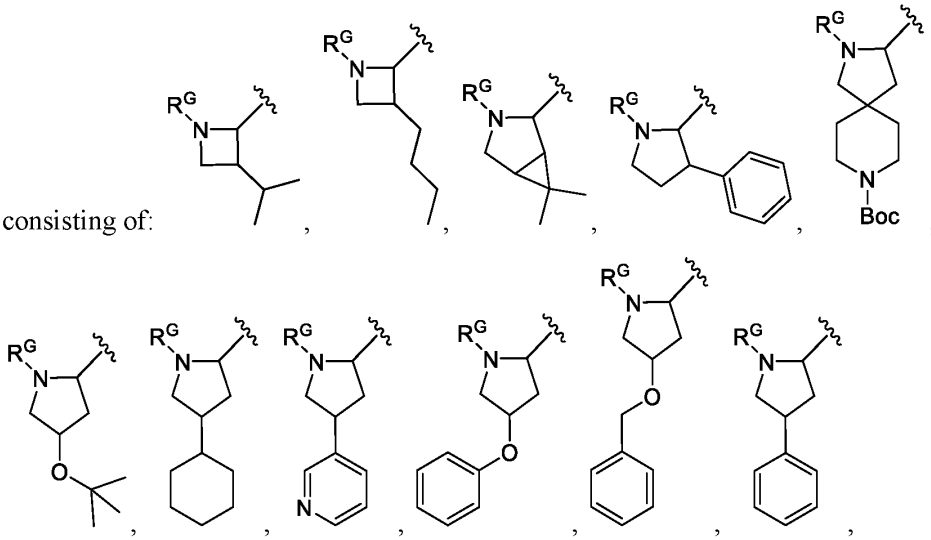
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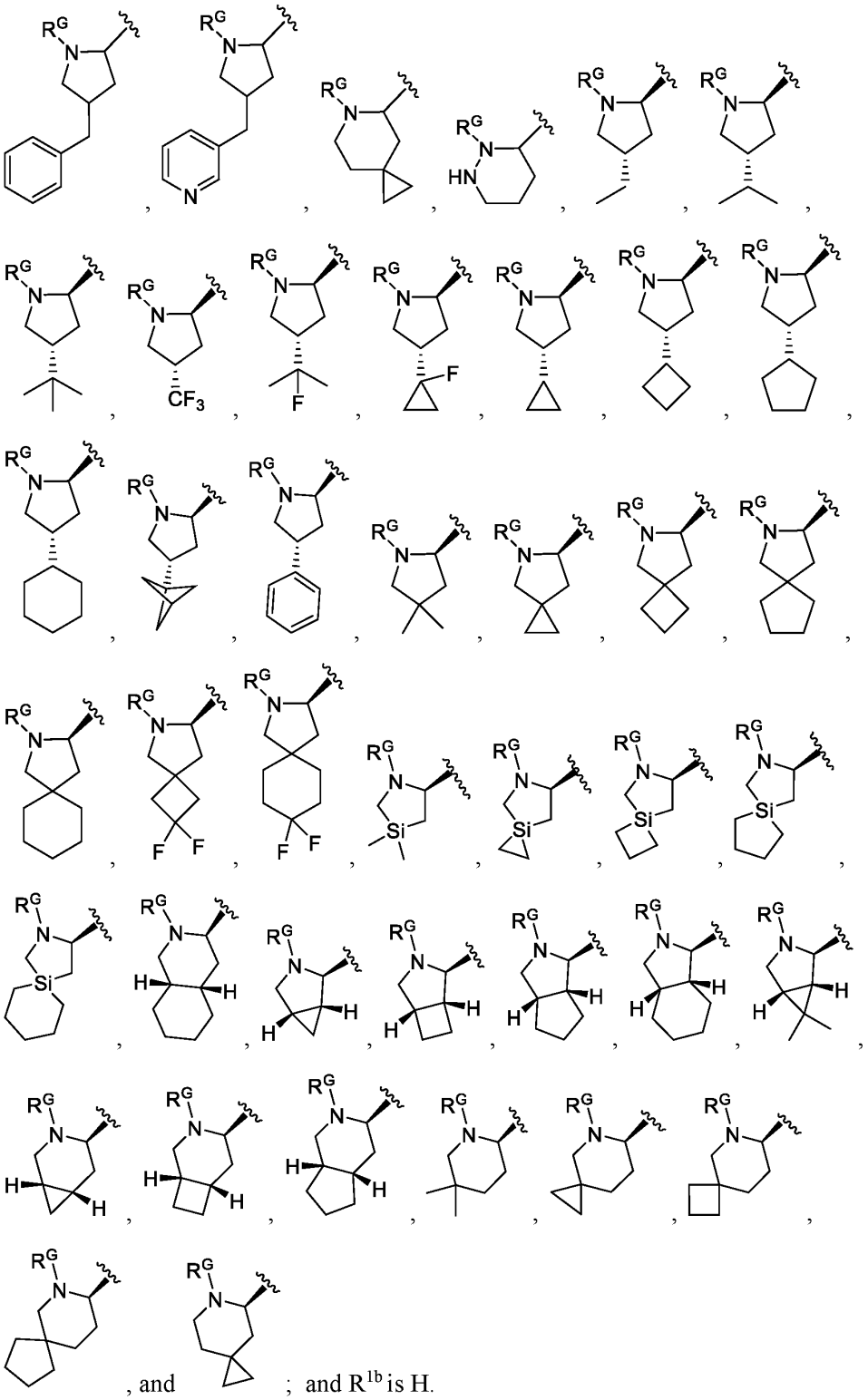
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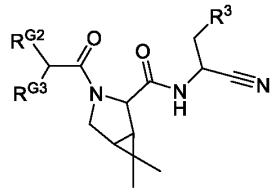
46. R^{1a} and R^2 are joined to together to form the heterocycle selected from the group consisting of:





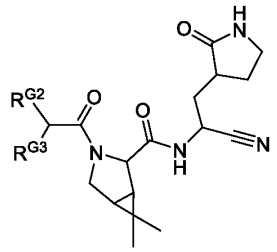
, and ; and R^{1b} is H.

48. The compound is represented by:



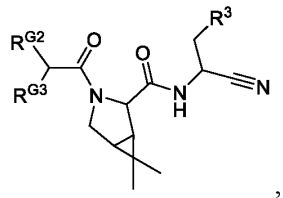
, wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, methyl or CF_3.

49. The compound is represented by:



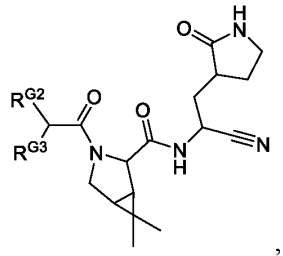
, wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, methyl or CF_3.

50. The compound is represented by:

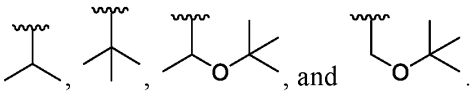


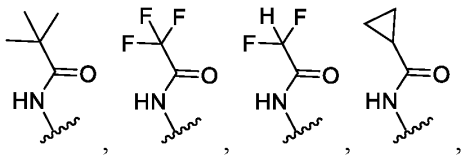
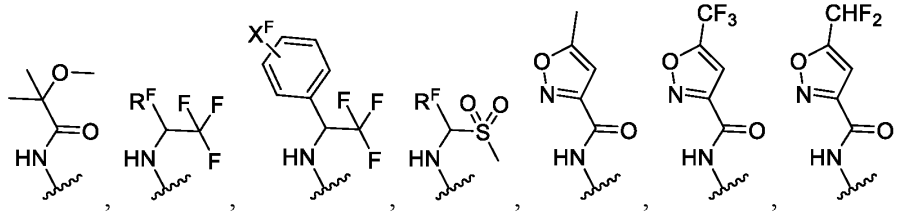
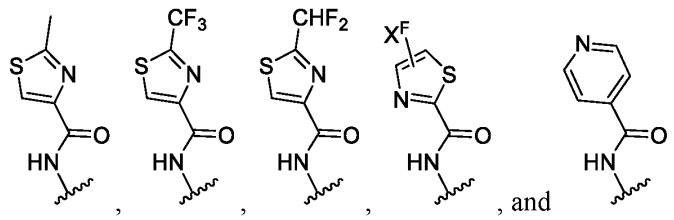
, wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three C_1-C_6alkoxy), C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is selected from the group consisting of -NH(C_{1-3}alkyl) (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, optionally substituted phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl) and -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), CHF_2, CF_3, or 5-6 membered heteroaryl (optionally substituted by halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, CHF_2, and CF_3).

51. The compound is represented by:



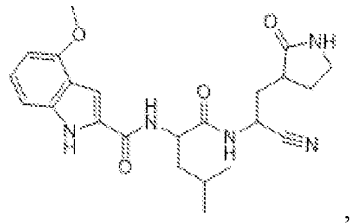
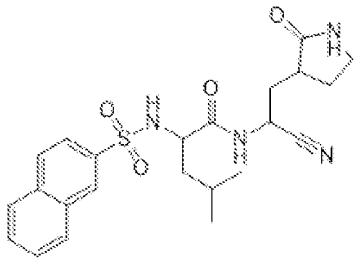
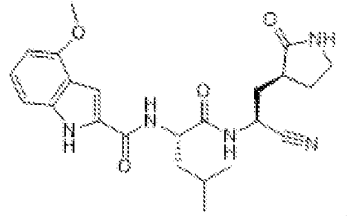
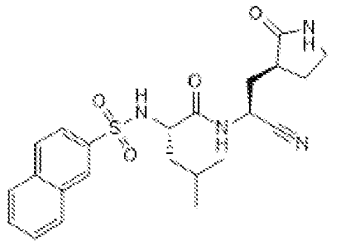
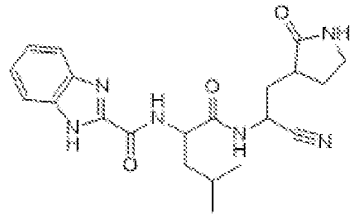
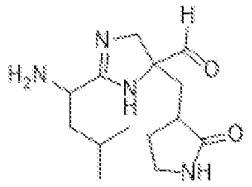
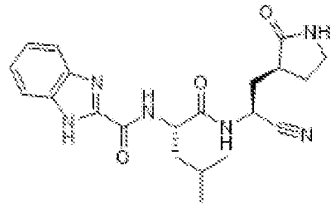
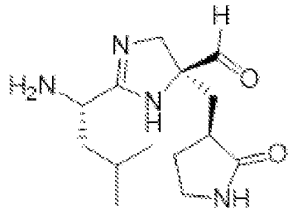
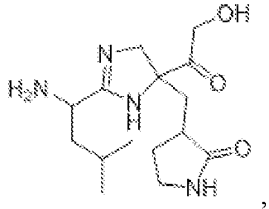
, wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three C_1-C_6alkoxy), C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is selected from the group consisting of -NH(C_{1-3}alkyl) (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, optionally substituted phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl) and -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), CHF_2, CF_3, or 5-6 membered heteroaryl (optionally substituted by halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, CHF_2, and CF_3).

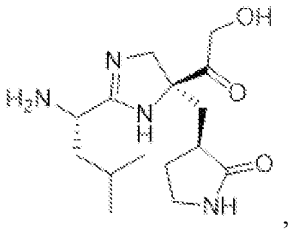
52. R^{G3} is selected from the group consisting of  .

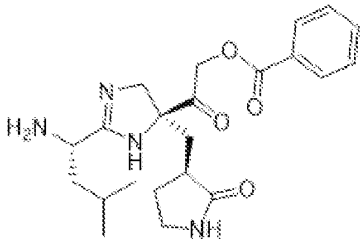
53. R^{G2} is selected from the group consisting of  ,  ,  , and ; wherein R^F is selected from the group consisting of C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and 5-6 membered

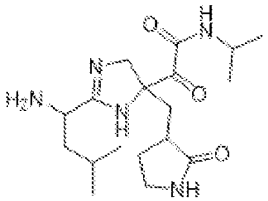
heteroaryl, wherein R^F may optionally be substituted by one, two or three substituents selected from the group consisting of halo, cyano, hydroxyl and C_1-C_6alkoxy; and X^F is selected from the group consisting of H, halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, and C_{1-6}haloalkyl.

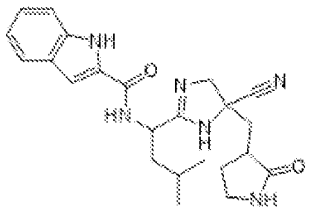
54. The compound is selected from the group consisting of:

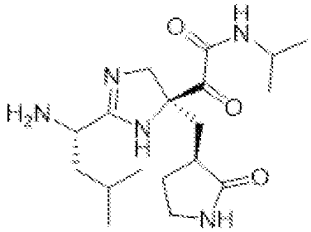

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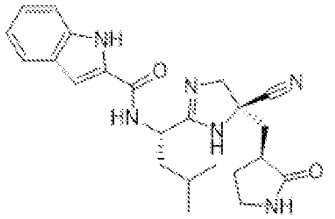

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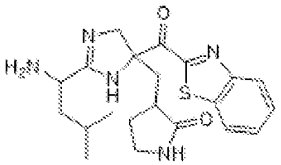

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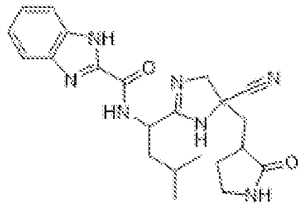

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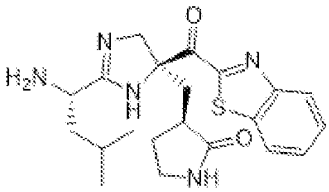

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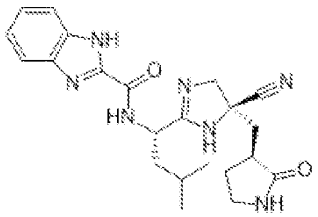

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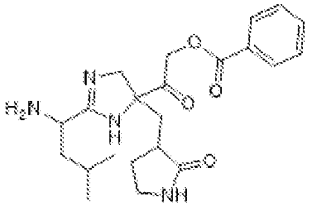

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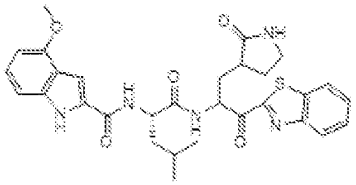

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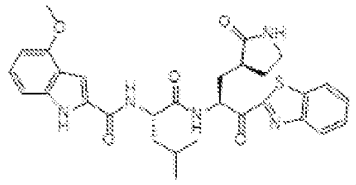

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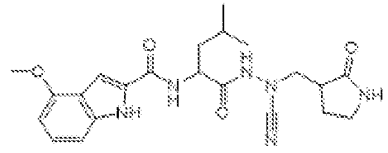

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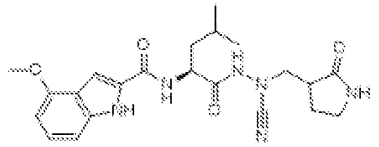

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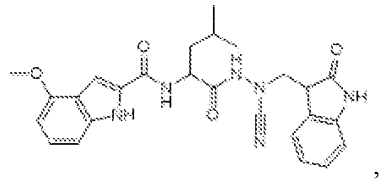
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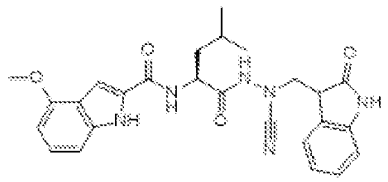
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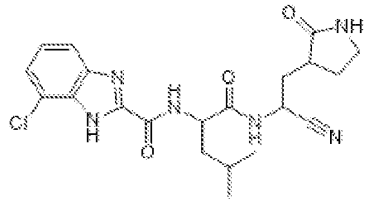
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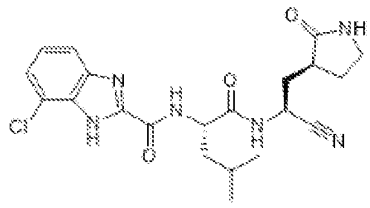
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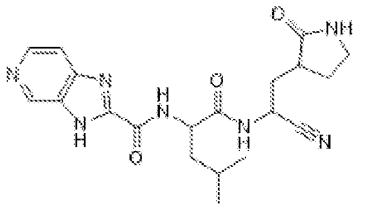
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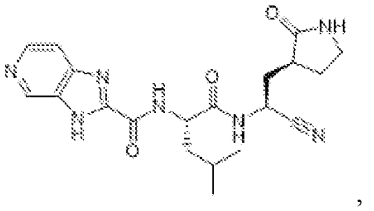
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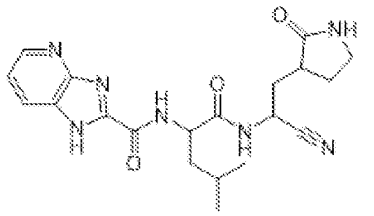
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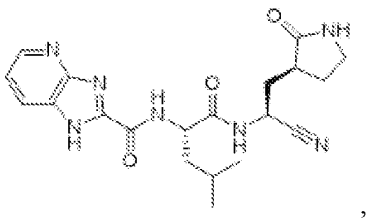
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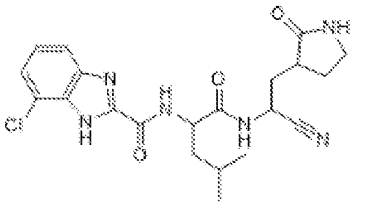
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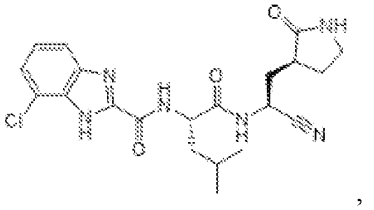
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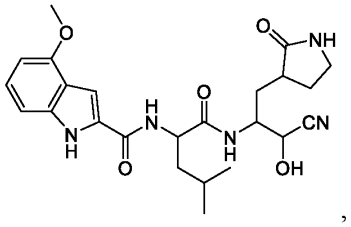
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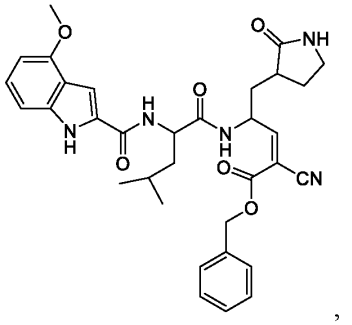
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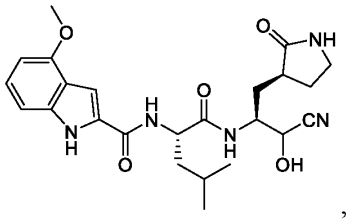
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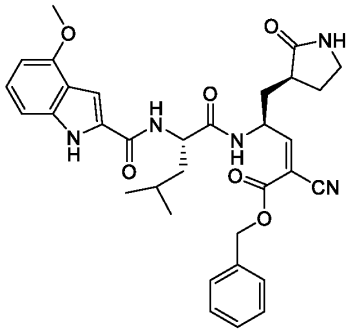
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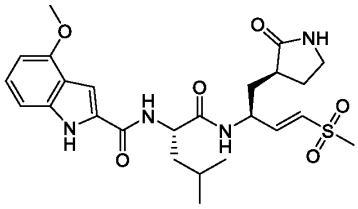
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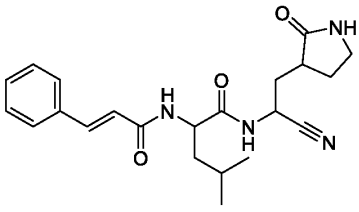
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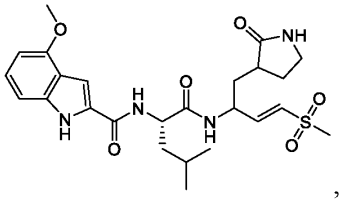
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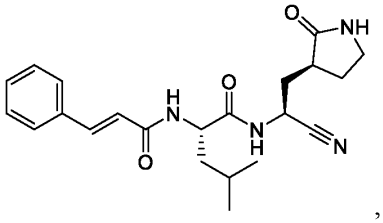
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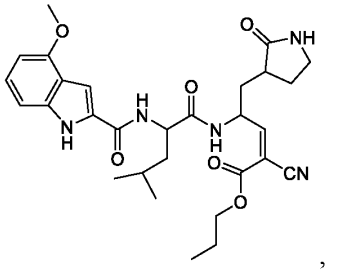
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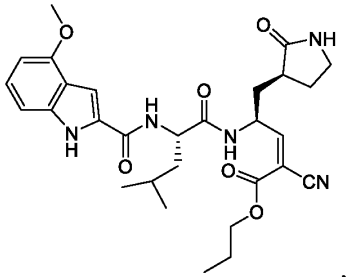


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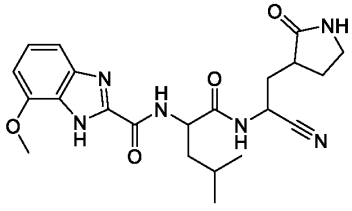


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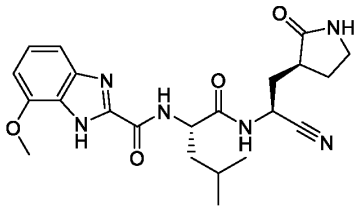
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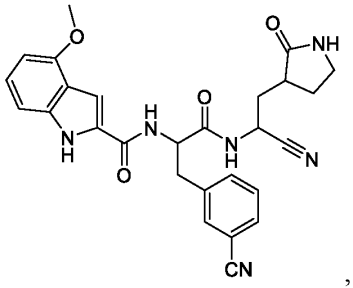


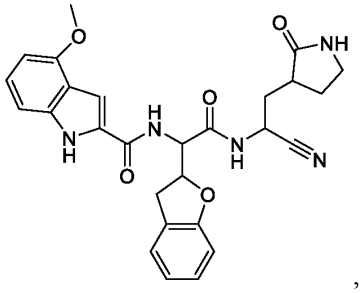
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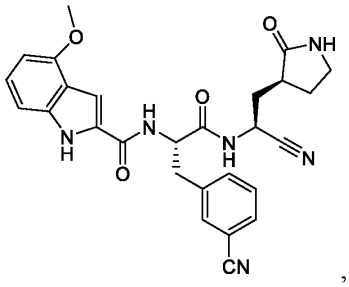


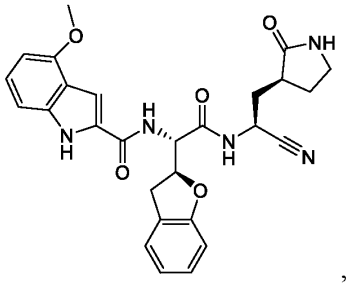
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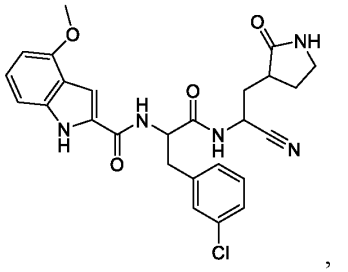

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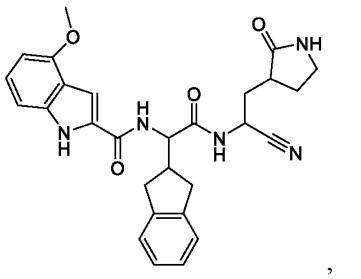

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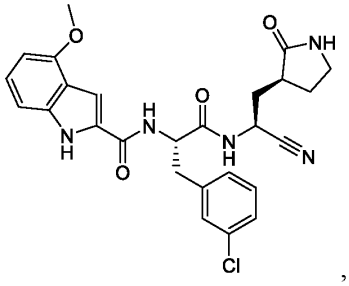

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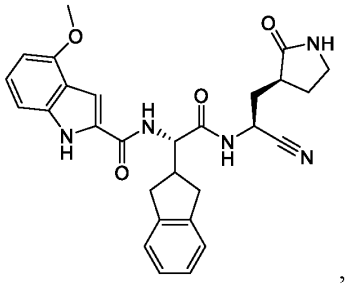

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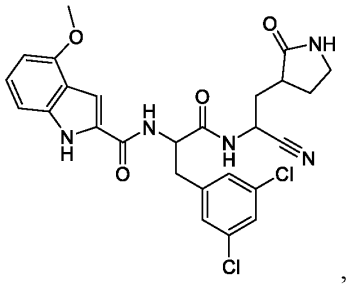

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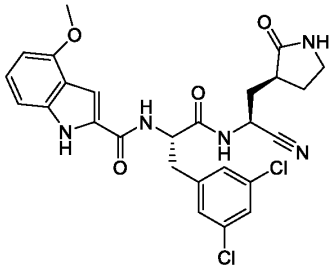

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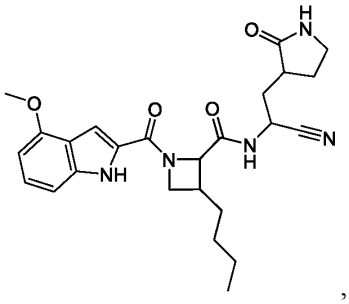

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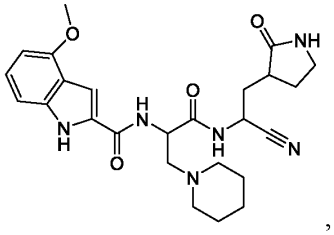

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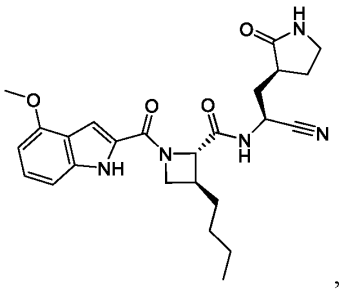
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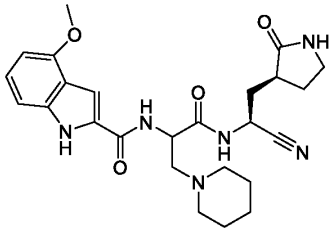
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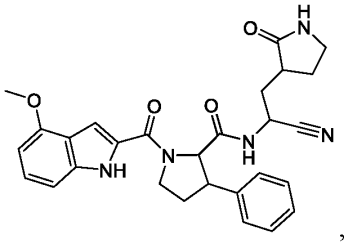
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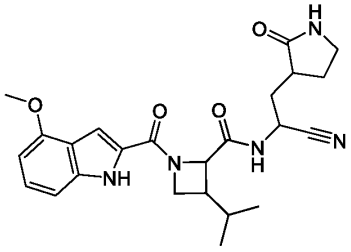
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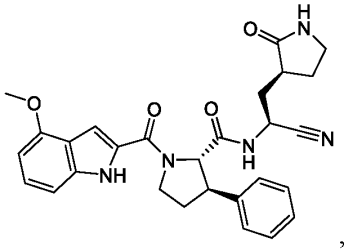
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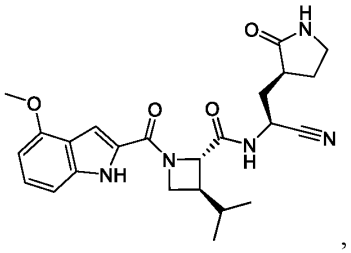
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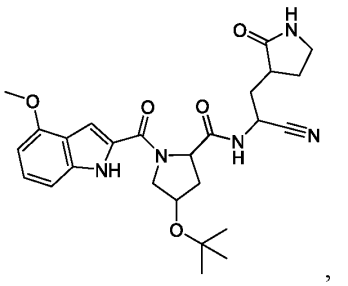
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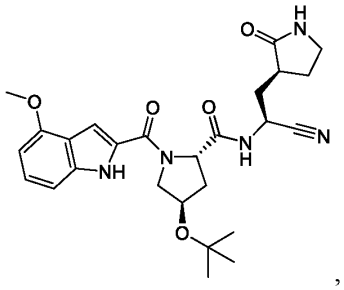
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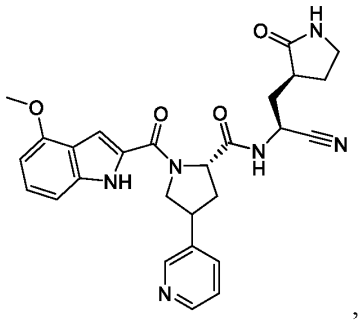
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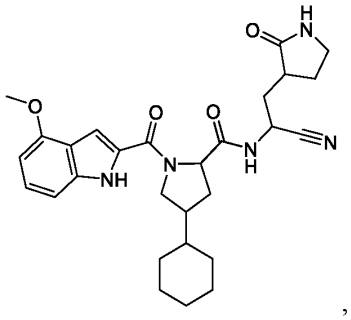
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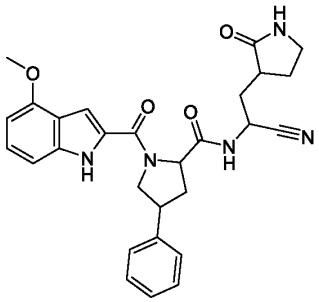
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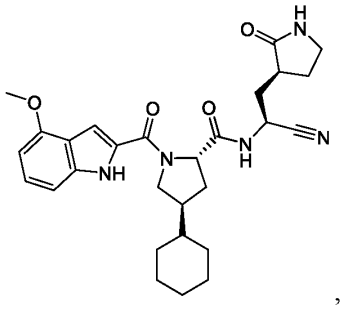
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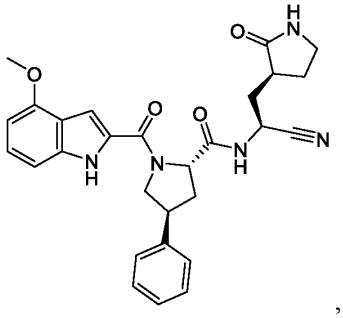
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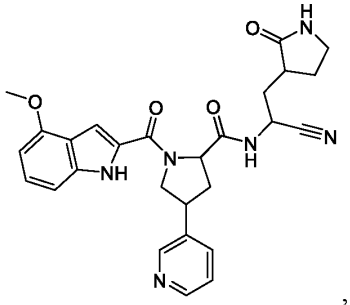
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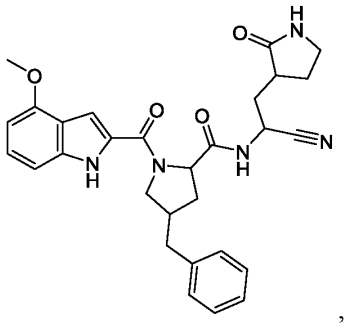
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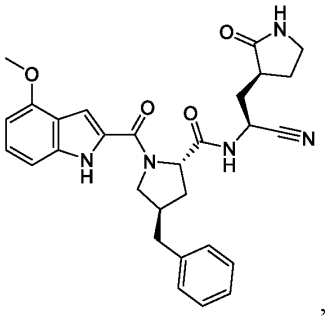
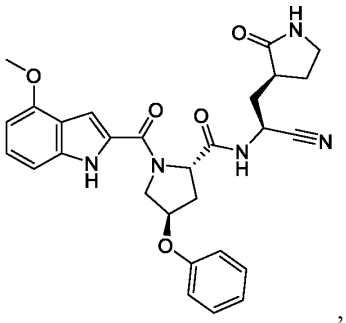
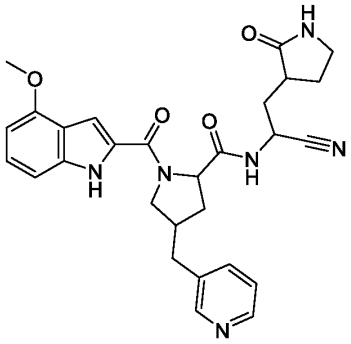
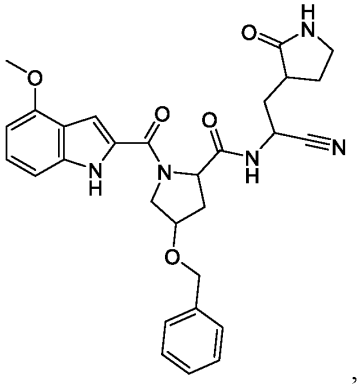
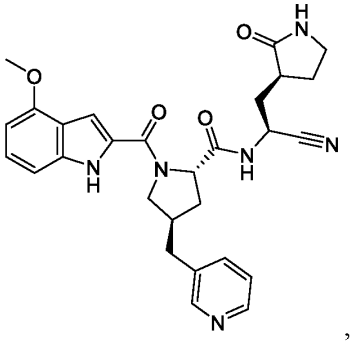
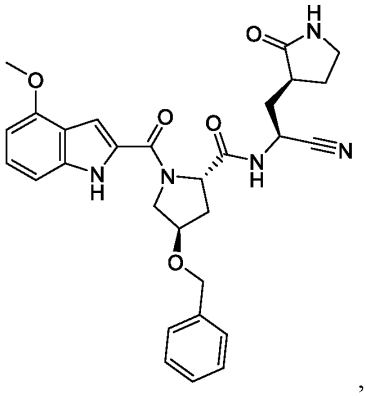
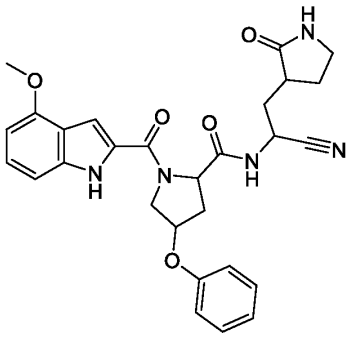
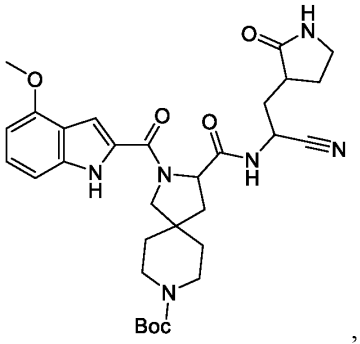
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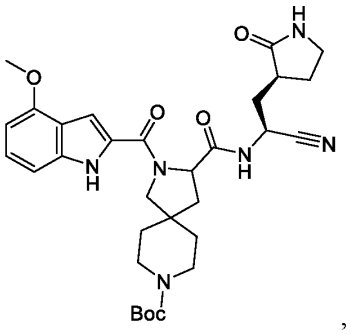


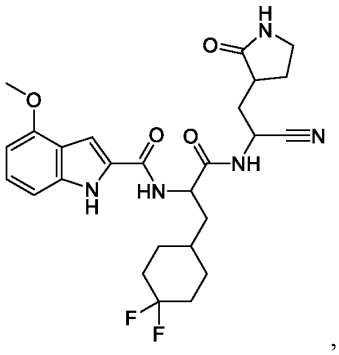
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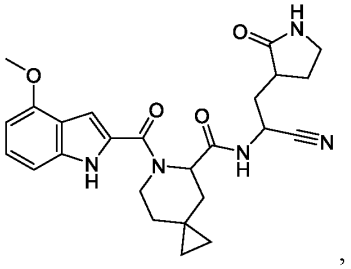


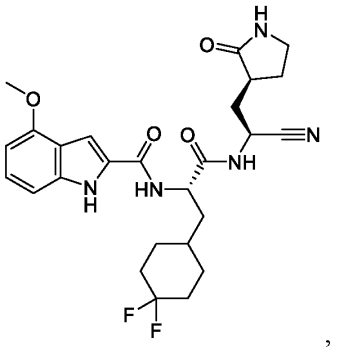
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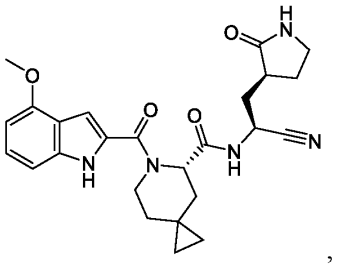

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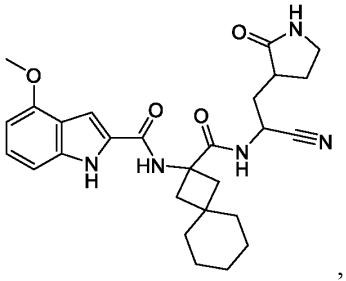

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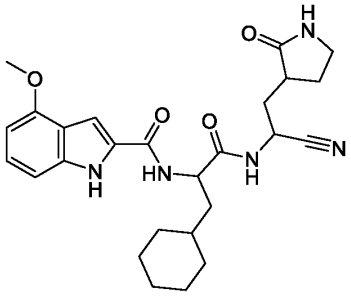

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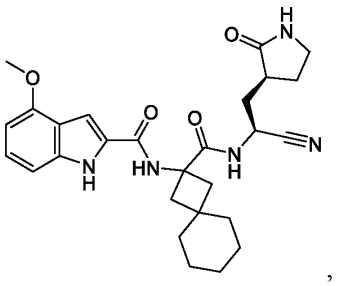

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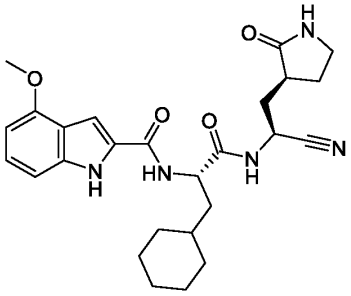

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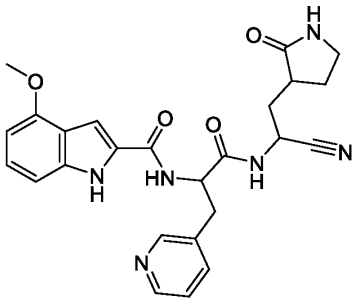

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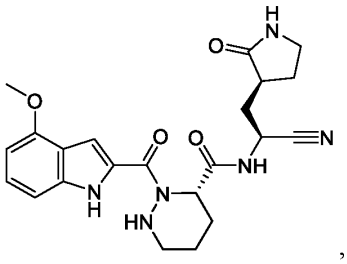

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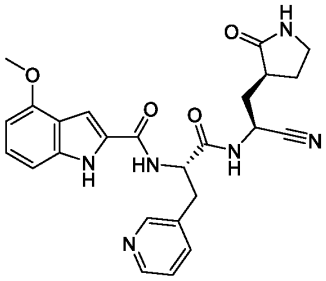

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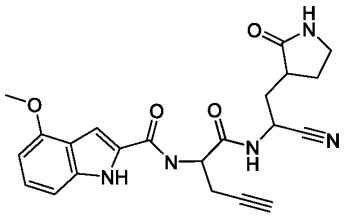

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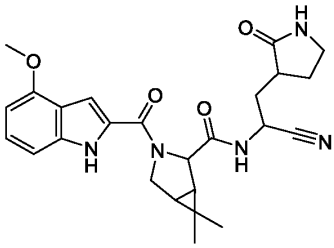

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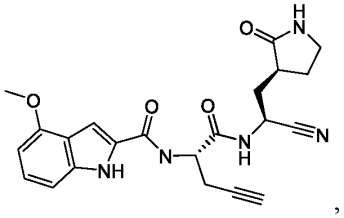

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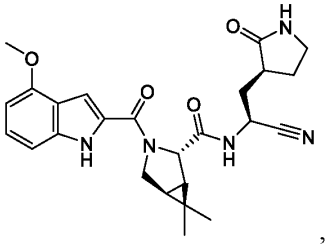

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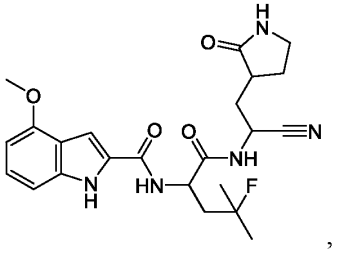

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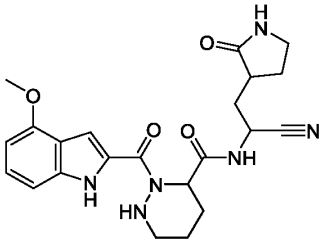

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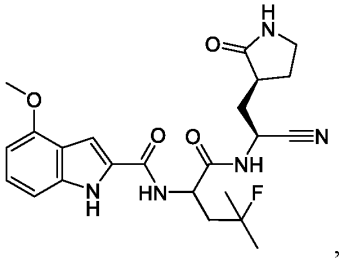

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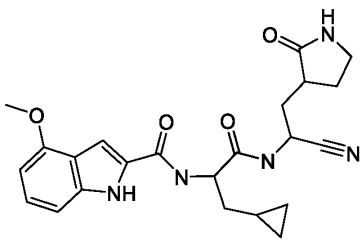

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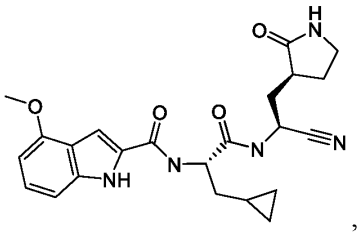

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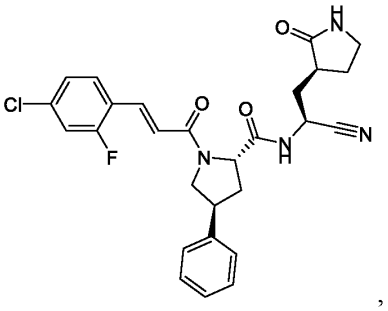
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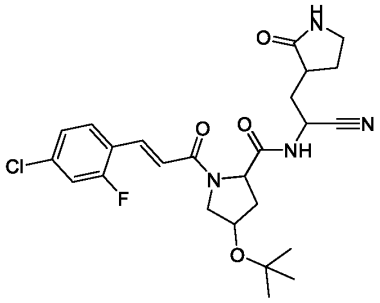
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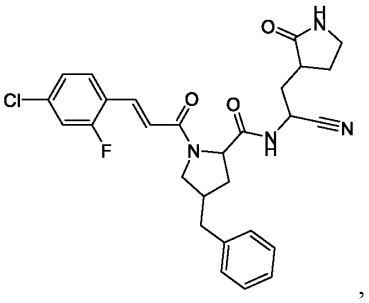
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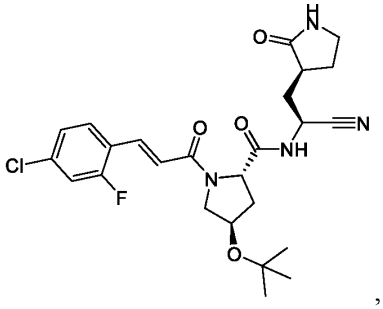
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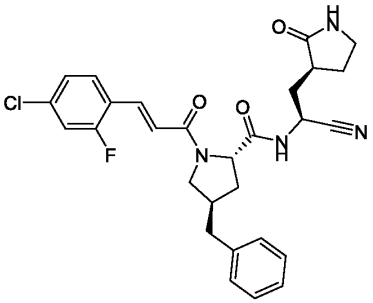
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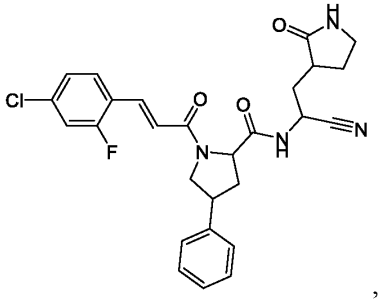
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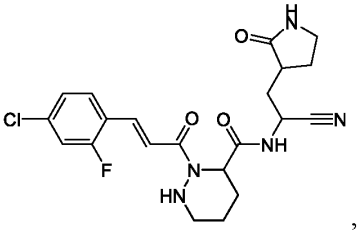
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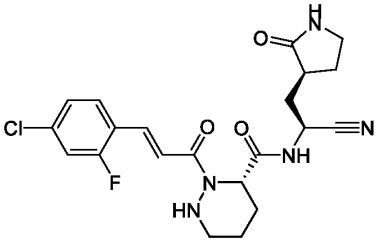
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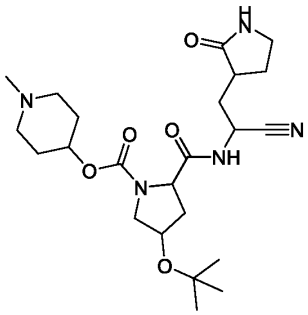
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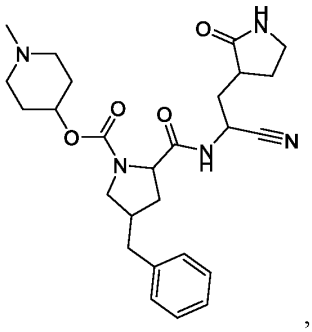
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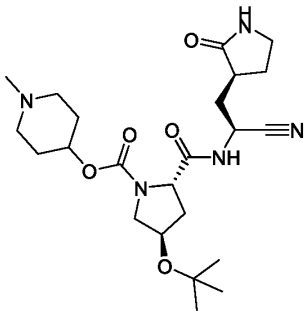
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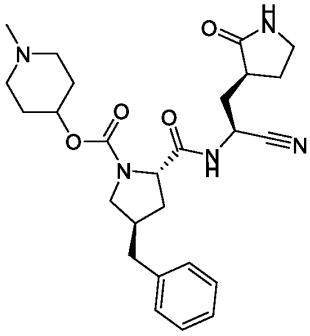
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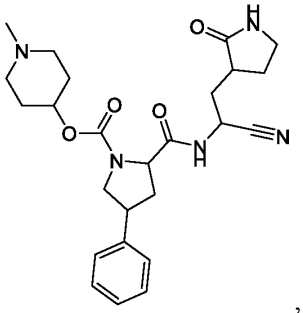
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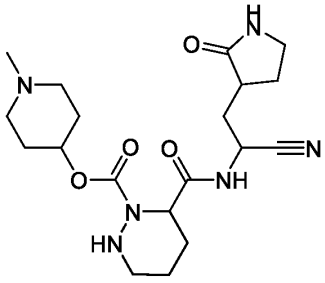
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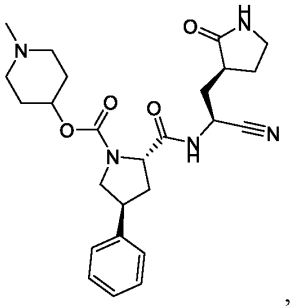
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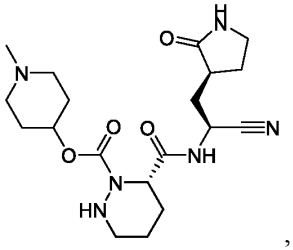
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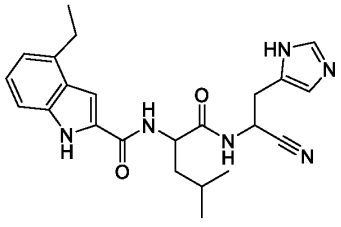
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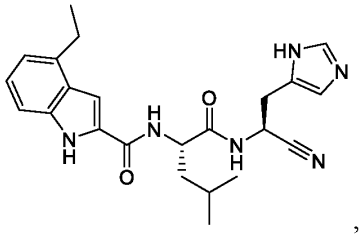
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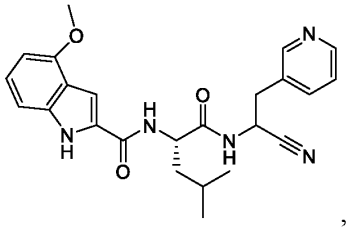
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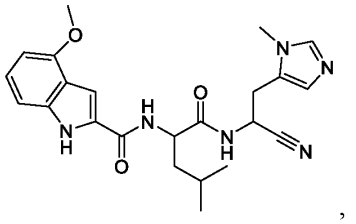
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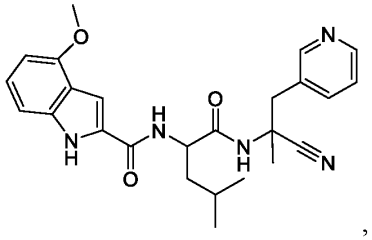
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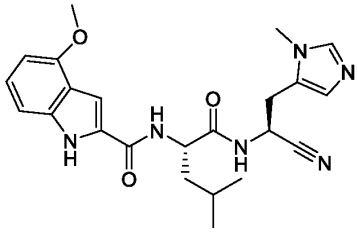
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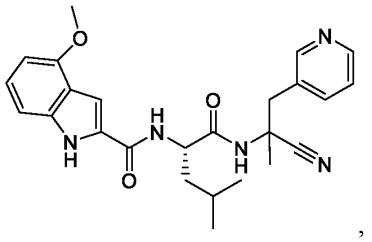
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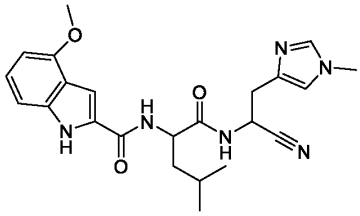
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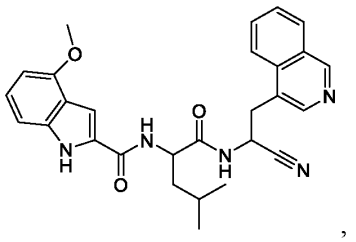
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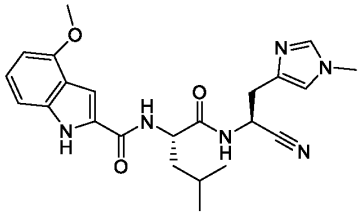
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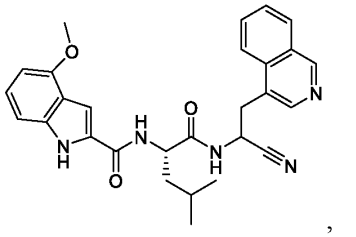
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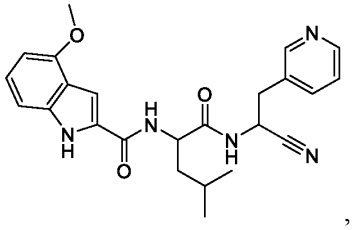
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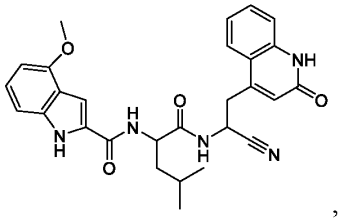
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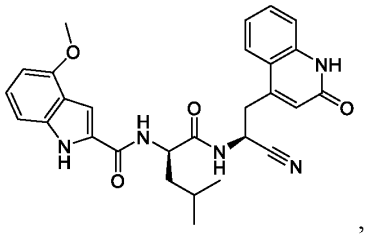
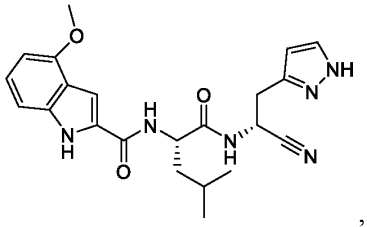
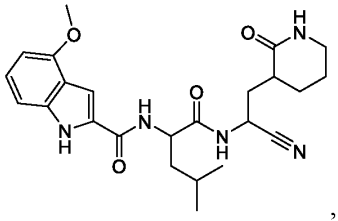
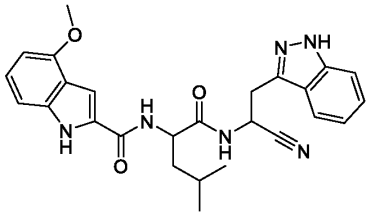
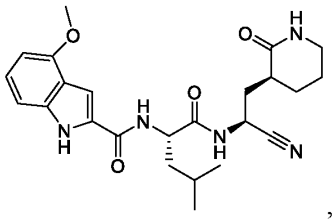
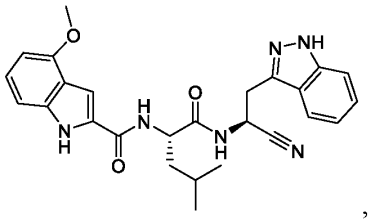
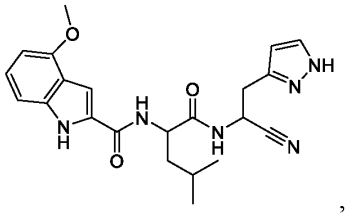
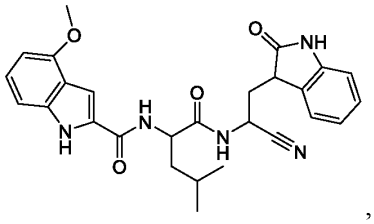
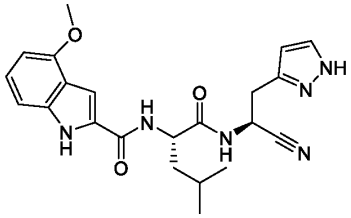
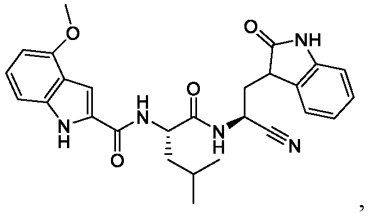
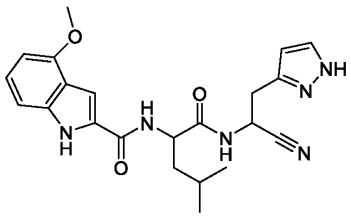
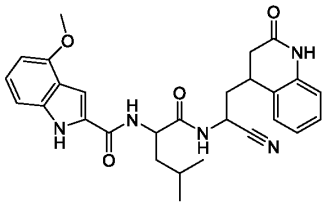


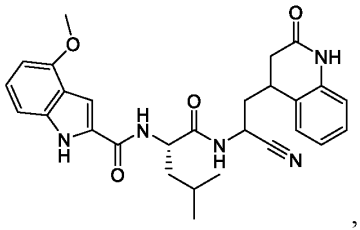
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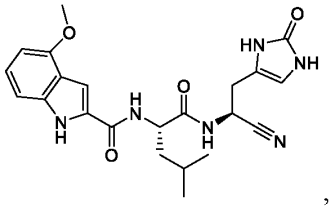
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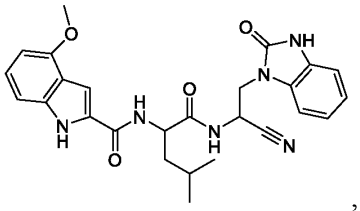

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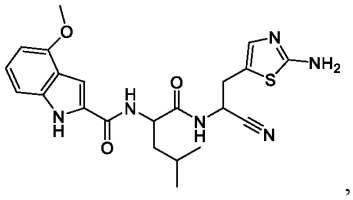
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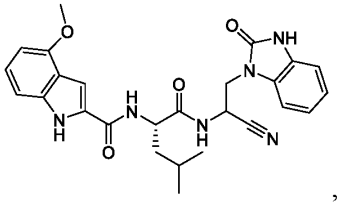
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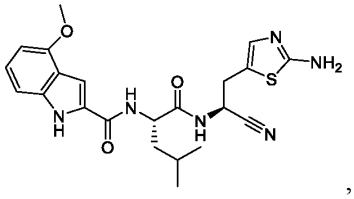
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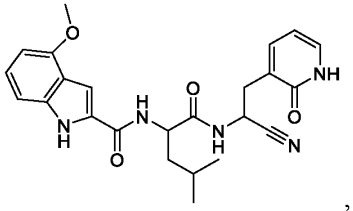
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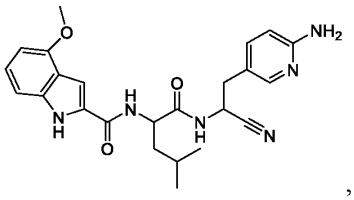
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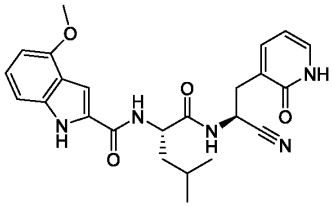
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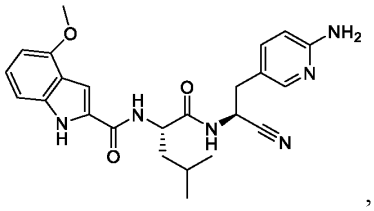
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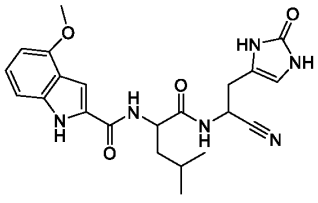
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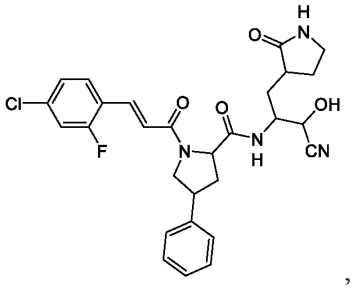
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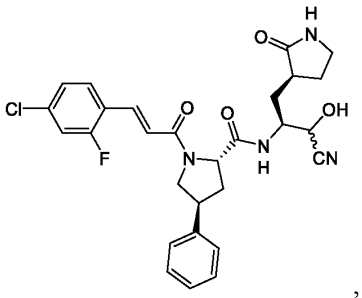
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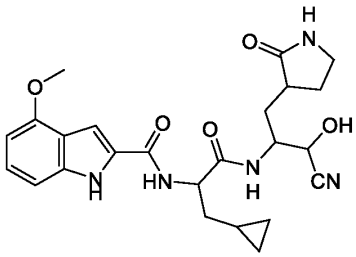
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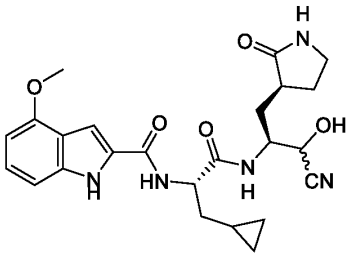
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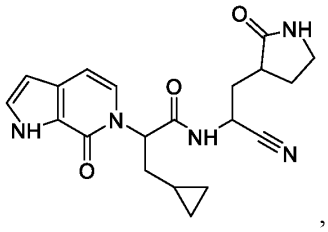
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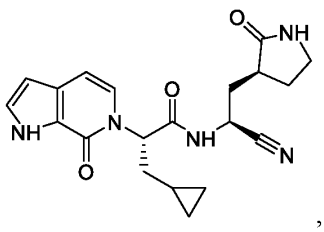
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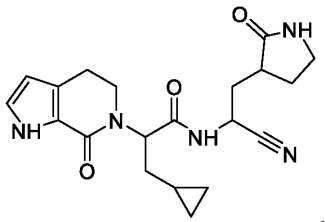
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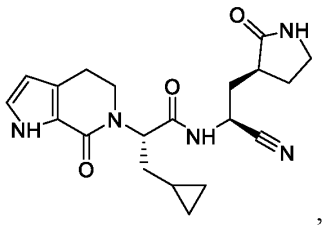
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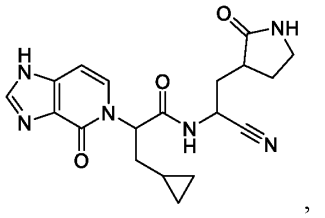
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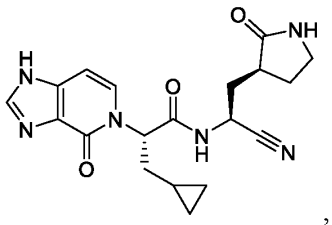
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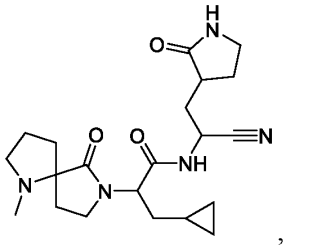
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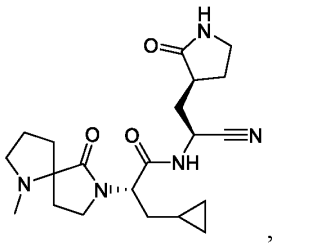
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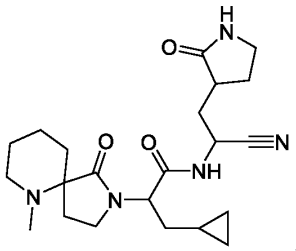
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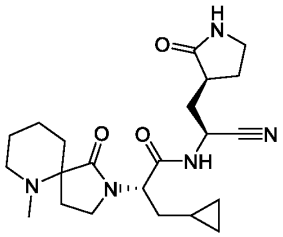
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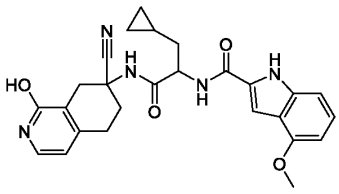
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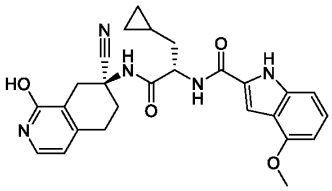
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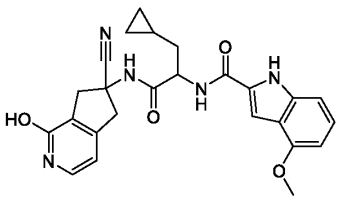
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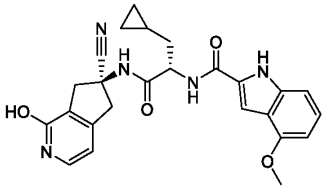
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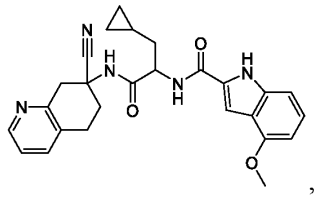
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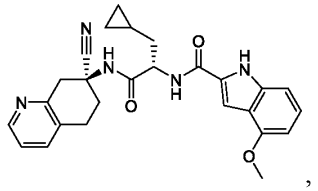
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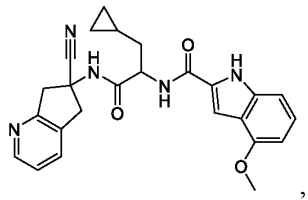
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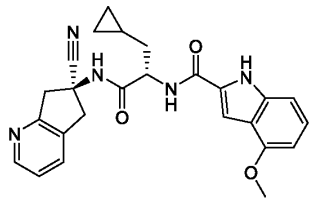
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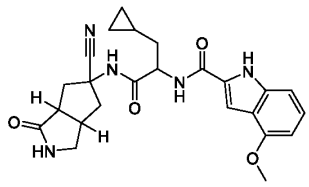
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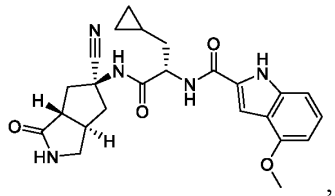
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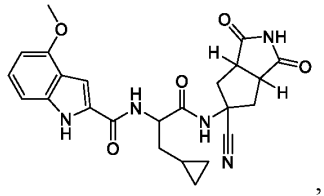
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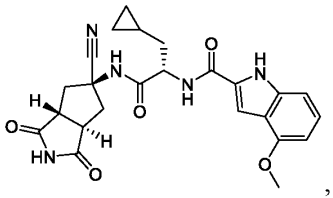
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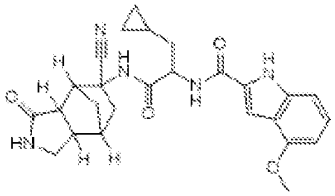
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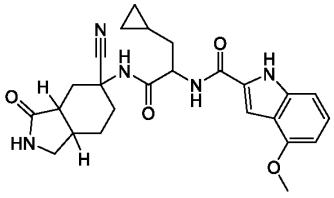
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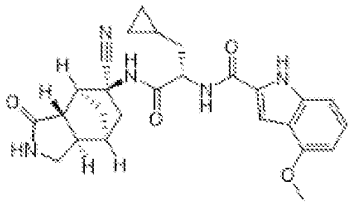
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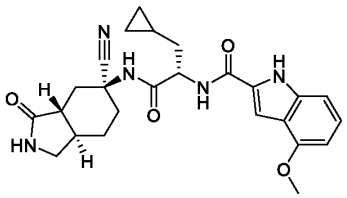
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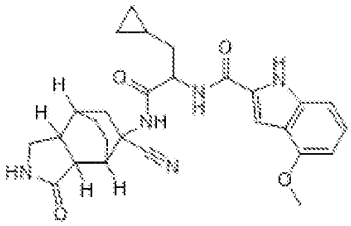
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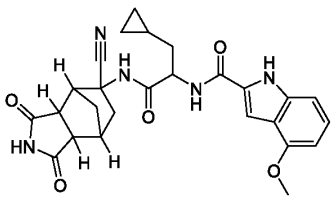
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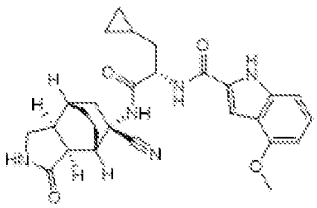
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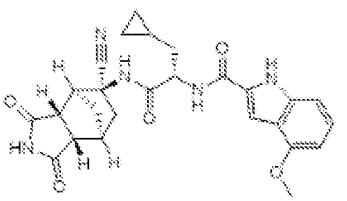
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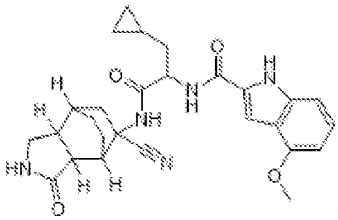
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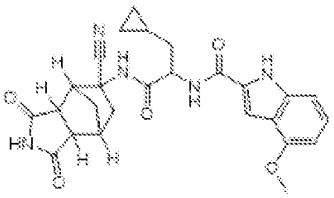
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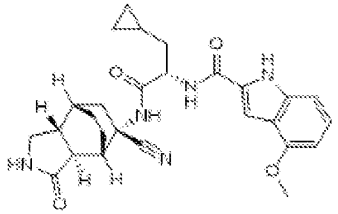
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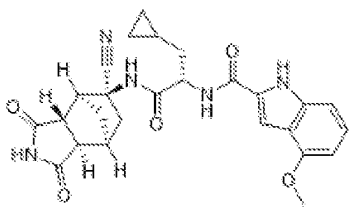
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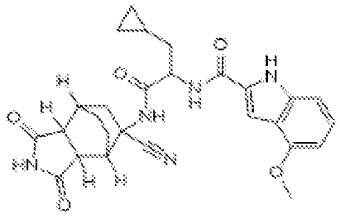
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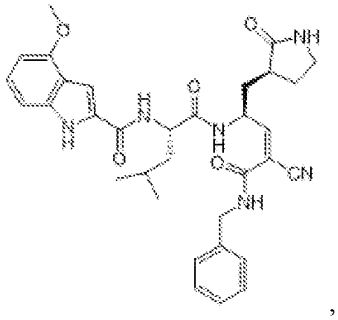
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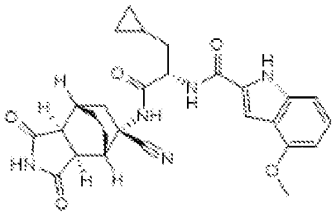
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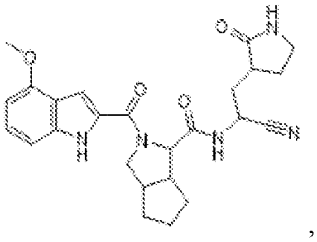
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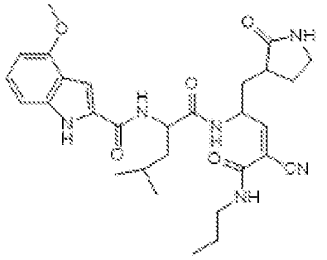
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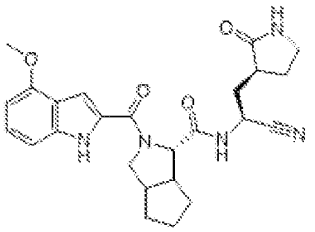
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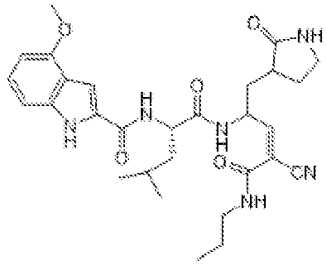
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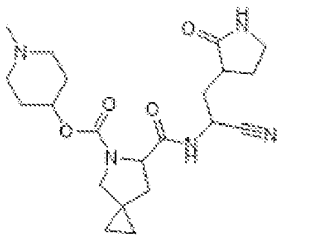
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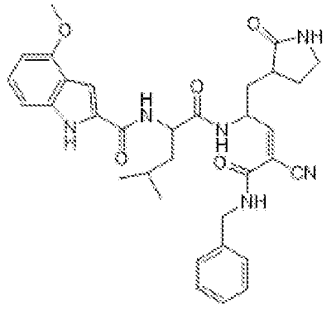
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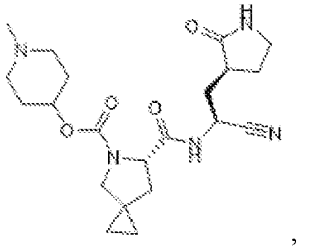
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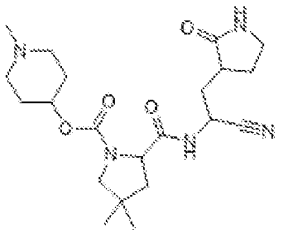
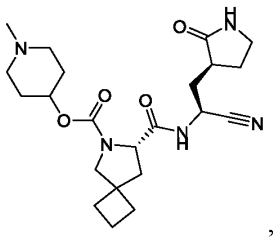
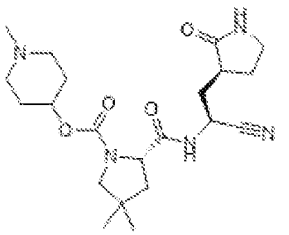
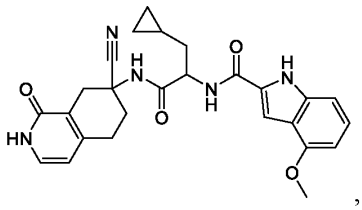
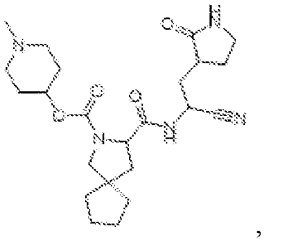
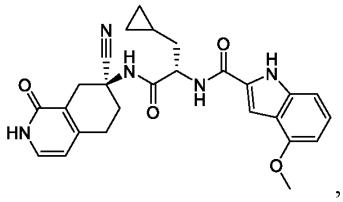
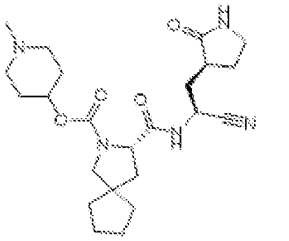
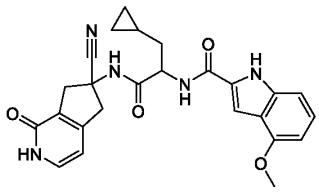
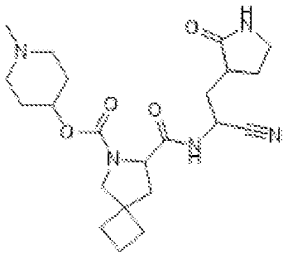
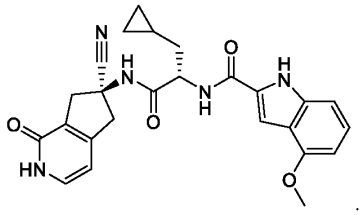
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55. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds of the embodiment.

56. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
57. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.
58. The viral infection is a coronavirus infection.
59. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).
60. The viral infection is SARS-CoV-2.
61. The viral infection is an arenavirus infection.
62. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.
63. The viral infection is an influenza infection.
64. The influenza is influenza H1N1, H3N2 or H5N1.
65. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of any compound of the embodiment to a patient suffering from the virus, and/or contacting an effective amount of any compound of the embodiment with a virally infected cell.
66. The method further comprises administering another therapeutic.
67. The method further comprises administering an additional anti-viral therapeutic.

68. The anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, and remdesivir.
69. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

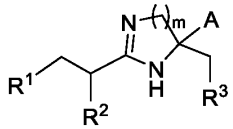
70. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, and remdesivir.

71. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of any compound of the embodiment.
72. The compound is administered before viral exposure
73. The compound is administered after viral exposure.

8. Contemplated Embodiment

[000197] In another aspect, the compositions, compounds and methods of the present disclosure may be described in another embodiment as follows:

1. A protease inhibitor compound represented by:



Formula I,

wherein:

R^1 is selected from the group consisting of and C_1-C_8alkyl, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–NH_2$, C_1-C_8alkyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

R^2 is selected from the group consisting of $–NH_2$, $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, 5-10 membered heterocycle, 5-10 membered aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, cyano, $–N(R^y)_2$, $–N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $–(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

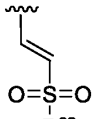
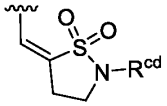
A is a warhead;

R^3 is selected from 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

m is 1 or 2; and

pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

2. A is selected from the group consisting of cyano, $–C(O)R^D$, $–C(O)CH_2N(R^bR^c)$, $–C(O)CH_2OC(O)R^D$, $–C(O)C(O)R^D$, $–(CH=CH)C(O)OR^D$, $–(CH=CCN)C(O)OR^D$, –

(CH=CCN)C(O)(NH)R^D, –CH(CN)(OH), -CH(CN)(NR^{b}R^c),  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} – N(R^bR^c), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

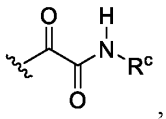
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

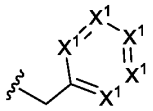
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

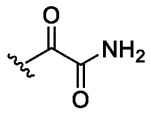
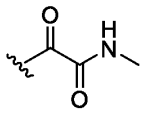
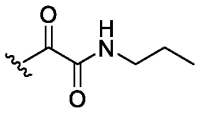
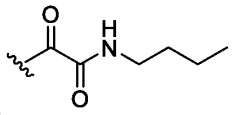
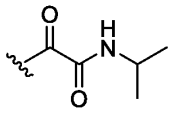
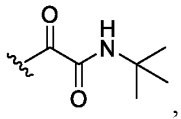
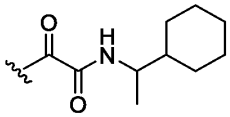
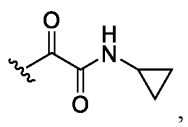
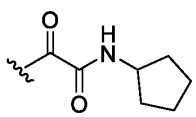
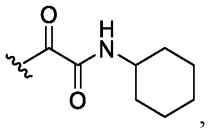
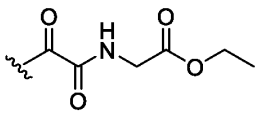
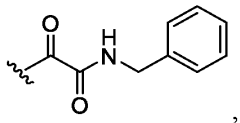
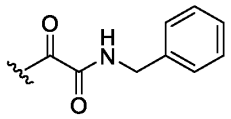
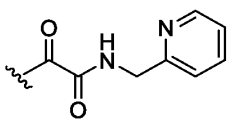
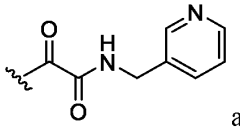
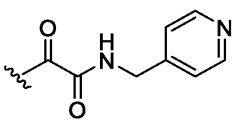
R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

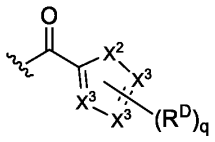
R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

3. A is a warhead represented by:  , wherein R^c is selected from the group consisting of hydrogen, $–CH_2C(O)O(C_1\text{-}C_8alkyl)$, $C_1\text{-}C_8alkyl$, and $C_3\text{-}C_6cycloalkyl$, wherein the $C_1\text{-}C_8alkyl$ may optionally be substituted by one or more substituents each selected from the group consisting of halogen, $C_3\text{-}C_6cycloalkyl$, 5-10 membered aryl and 5-10 membered heteroaryl.

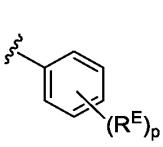
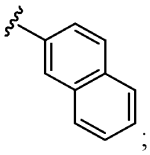
4. R^c is  , wherein X^1 is independently selected, for each occurrence, from N and CH.

5. A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

6. A is  , wherein

X^2 is selected from the group consisting of NH, O and S;

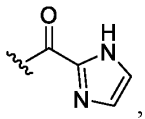
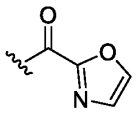
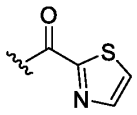
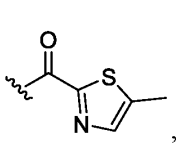
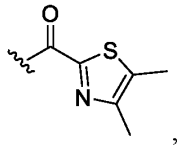
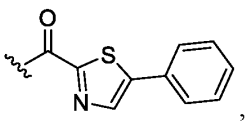
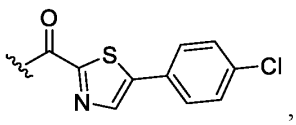
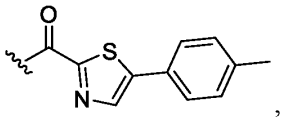
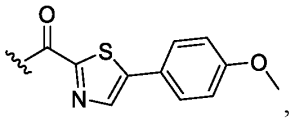
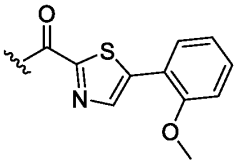
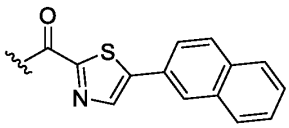
X^3 is independently selected, for each occurrence, from N and CH;

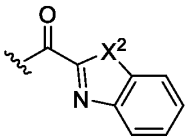
R^D is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl,  and  ;

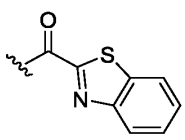
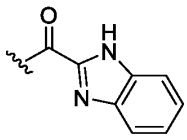
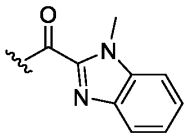
R^E is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, C_1-C_8alkyl and C_1-C_8alkoxy;

p is selected from 0, 1 and 2; and

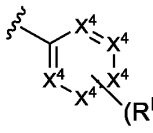
q is selected from 0, 1 and 2.

7. A is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

8. A is  , wherein X^2 is selected from the group consisting of NH, NR^P, O and S, wherein R^P is C_1-C_8alkyl.

9. A is selected from the group consisting of  ,  and  .

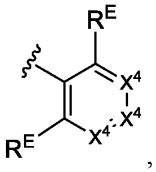
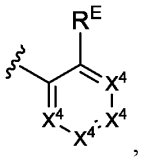
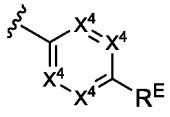
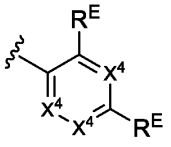
10. A is–$C(O)CH_2OC(O)R^D$, wherein

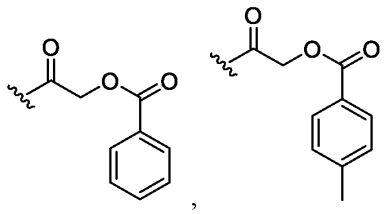
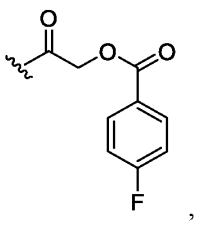
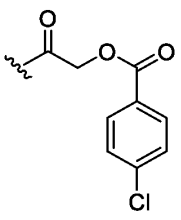
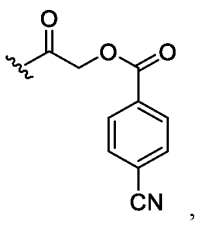
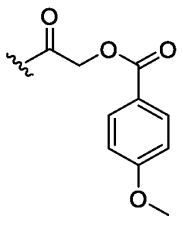
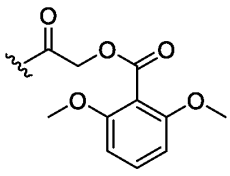
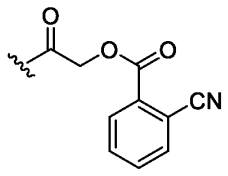
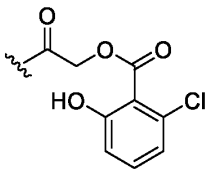
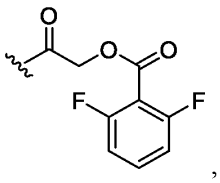
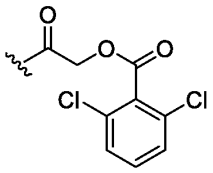
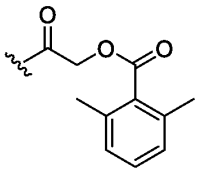
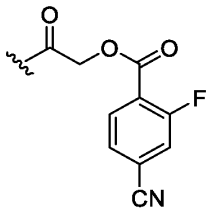
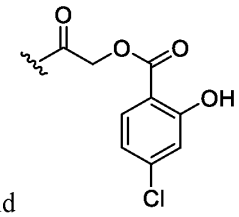
R^D is selected from the group consisting of  , C_1-C_8alkyl and C_3-C_6cycloalkyl;

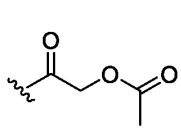
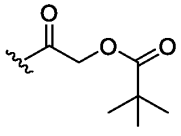
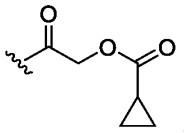
X^4 is independently selected, for each occurrence, from CH and N;

R^E is independently selected, for each occurrence, from the group consisting of halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-CF_3$, $-OCF_3$ and $-SCF_3$; and

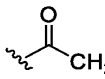
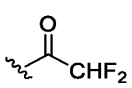
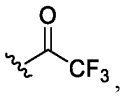
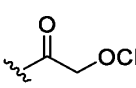
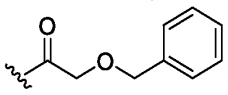
p is selected from 0, 1 and 2.

11. R^D is selected from the group consisting of  ,  ,  and  .

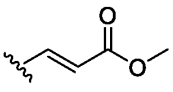
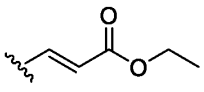
12. A is selected from the group consisting of  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

13. A is selected from the group consisting of  ,  and  .

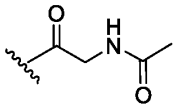
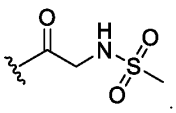
14. A is–C(O)R^D, wherein R^D is selected from the group consisting of hydrogen, –CH_2OH, -CH_2OR' and –CH_xF_y, wherein R' is selected from the group consisting of C_1-C_8alkyl, -(C_1-C_8alkyl)-(5-10 membered aryl), C_1-C_8heteroalkyl, C_3-C_6cycloalkyl and 5-10 membered aryl, wherein x is 0, 1 or 2; y is 1, 2 or 3; and the sum of x and y is 3.

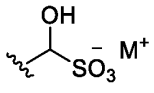
15. A is selected from the group consisting of  ,  ,  ,  ,  ,  and  .

16. A is –(CH=CH)C(O)OR^D, wherein R^D is C$_1$-C$_8$alkyl.

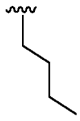
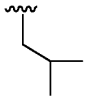
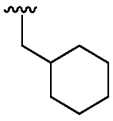
17. A is selected from  and  .

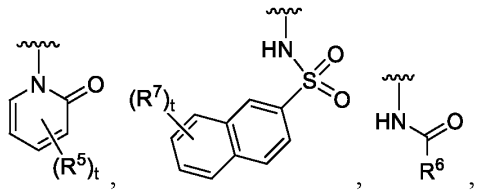
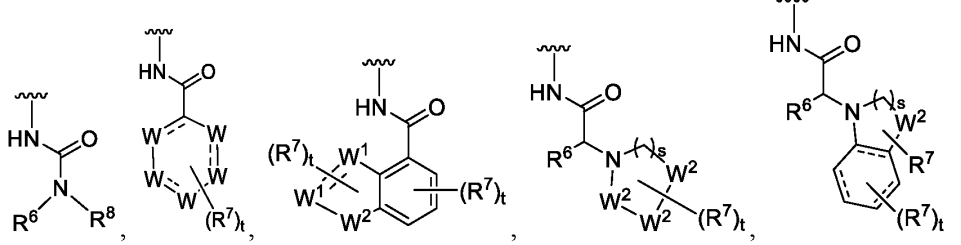
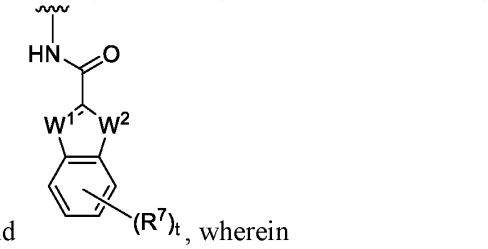
18. A is–C(O)CH$_2$N(R^{b}R^c).

19. A is a warhead selected from  and  .

20. A is  , wherein M is selected from Na and K.

21. A is cyano.

22. R^1 is selected from the group consisting of  ,  ,  and  .

23. R^2 is selected from the group consisting of  ,  ,  , , and , wherein

 denotes a bond that may be a single or double bond;

R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^6 is C_1-C_8alkyl;

R^7 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, $-(C_1$-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

R^8 is selected from the group consisting of 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle;

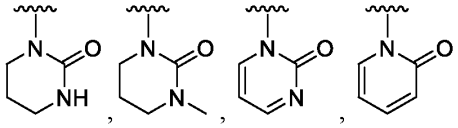
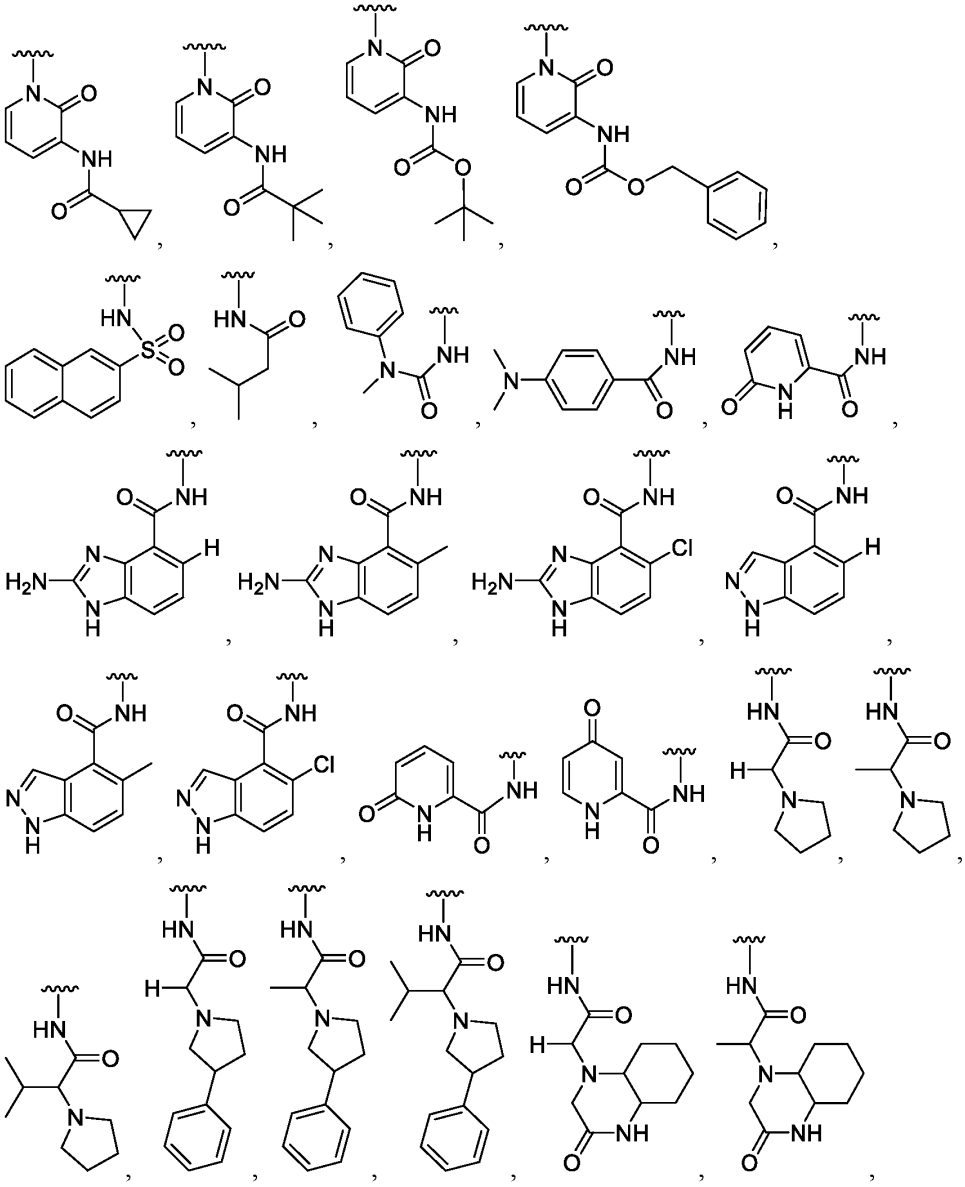
W^1 is selected from CH and N;

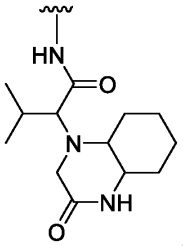
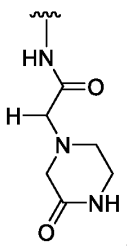
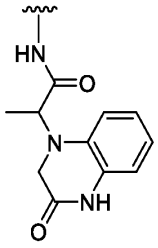
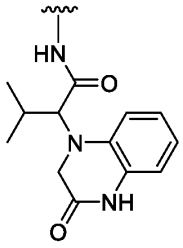
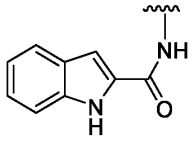
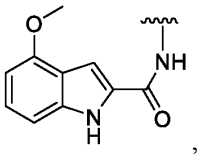
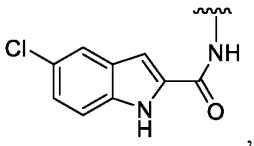
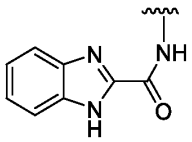
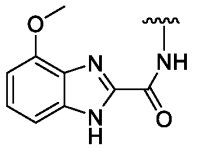
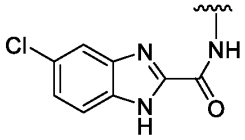
W^2 is selected from the group consisting of CH_2, O, NH and S;

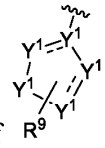
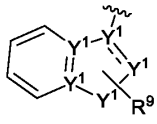
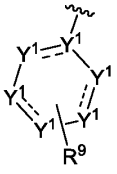
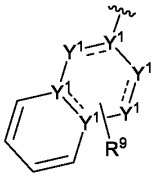
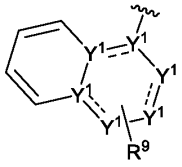
W is selected from W^1 and W^2;

s is selected from 1 and 2; and

t is selected from 0, 1, 2 and 3.

24. R^2 is selected from the group consisting of  , 


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and

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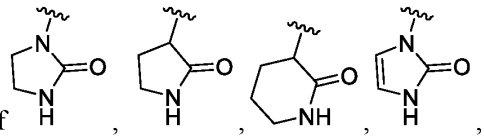
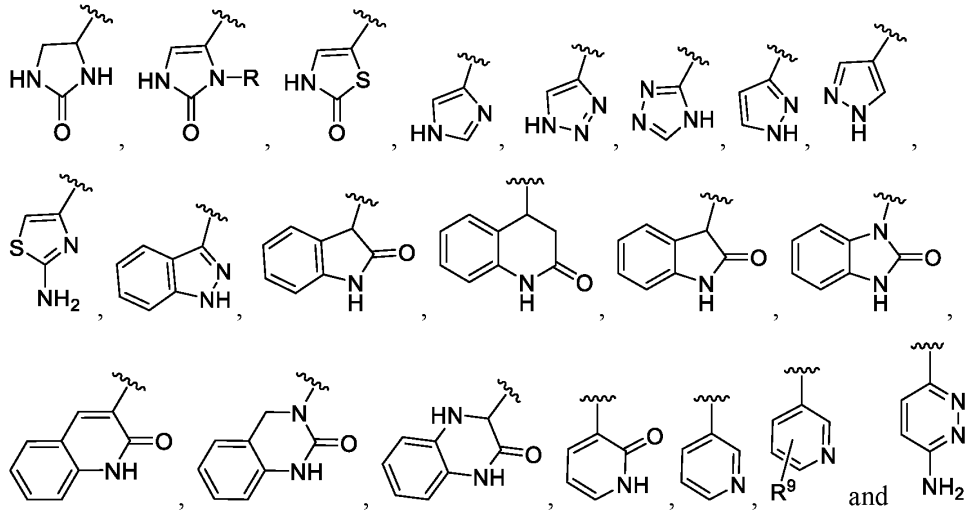
25. R^3 is selected from the group consisting of

,

,

,

,

,

wherein

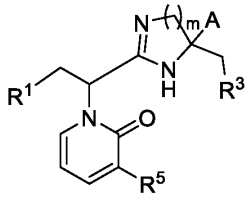
$=\!=\!=\!=\!=\!=\!=$ denotes a bond that may be a single or double bond;

Y^1 is selected from the group consisting of CH, CH_2, N, NH, O and S;

R^9 is selected from the group consisting of halogen, hydroxyl, oxo, $–NH_2$, $–N(CH_3)_2$, $–N(CH_2CH_3)_2$, $–CH_3$, $–CH_2CH_3$, $–OCH_3$ and $–OCH_2CH_3$.

26. R^3 is selected from the group consisting of  ,  , and .

27. The compound is represented by



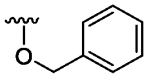
Formula I-A,

wherein:

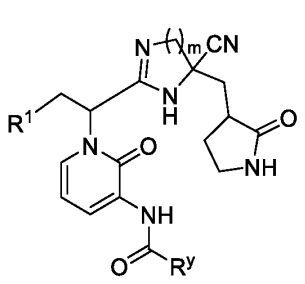
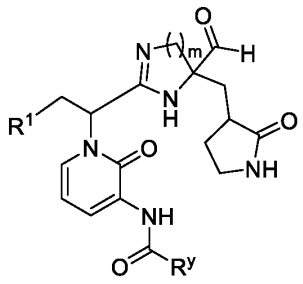
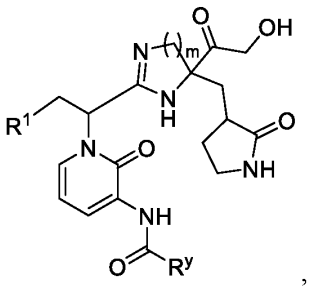
R^5 is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, $-N(R^y)C(O)R^y$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

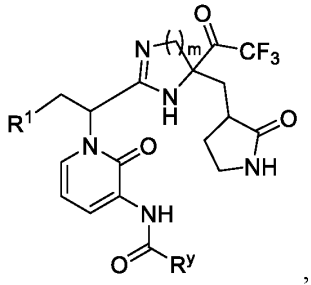
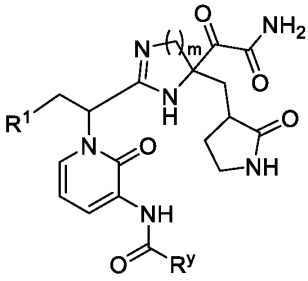
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl; and

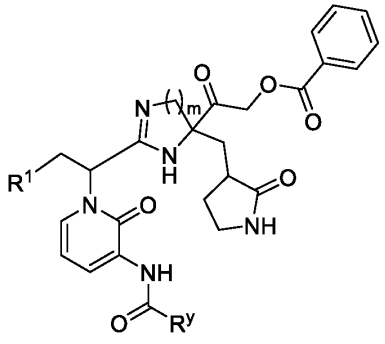
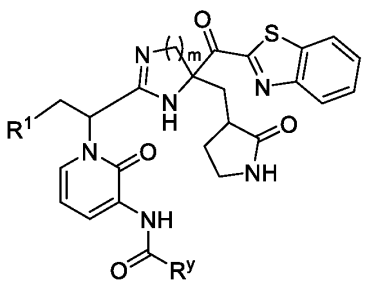
m is selected from 1 and 2.

28. R^y is selected from the group consisting of hydrogen,  ,  ,  and  .

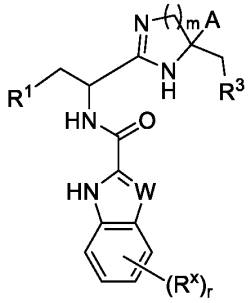
29. The compound is selected from the group consisting of:

 ,  ,  ,

 ,  ,

 , and  .

30. The compound is represented by



Formula I-B,

wherein

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, $-N(R^y)_2$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, 5-10 membered aryl, 5-10 membered heteroaryl and 5-10 membered heterocycle, wherein the heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy and C_3-C_6cycloalkyl;

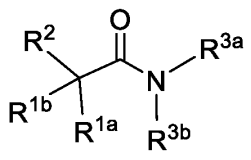
W is CH or N;

m is selected from 1 and 2; and

r is selected from 0, 1, 2 and 3.

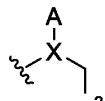
31. R^x is $-OCH_3$.

32. A protease inhibitor compound represented by:



Formula II,

wherein

R^{3a} is selected from  and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of C_1-C_8alkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl; or

R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–NH_2$, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocycle), –C(O)-O-(4-10 membered heterocycle), $–C(O)-OC(CH_3)_3$, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the alkyl, cycloalkyl, heterocycle, heteroaryl, or aryl may optionally be substituted by one, two or three substituents of halogen, C_1-C_6alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl or oxo;

R^2 is selected from the group consisting of –NHC(O)R^B, –NHC(O)N(R^B)$_2$, –NHC(O)C(R^C)$_2$$R^B$, –NHS(O)$_2$$R^B$, 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^2 may optionally be substituted by one, two, or three substituents each selected from R^x; or

R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered mono or bicyclic heterocycle having a ring nitrogen, NR^G, or C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen and C_1-C_8alkyl;

R^G is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m) and C(=O)-C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocycle, C_1-C_6alkoxy, wherein R^m is selected for each occurrence by H, C_{1-3}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, optionally substituted phenyl, -S(O)$_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl), C(=O)-C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), C(=O)-C_{3-6}cycloalkyl, or

C(=O)-(5-6 membered heteroaryl) (optionally substituted by halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, and C_{1-6}haloalkyl));

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, SF_5, cyano, –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo and C_1-C_8alkyl;

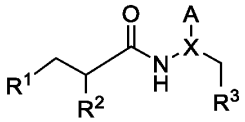
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl) and C_3-C_6cycloalkyl;

A is a warhead;

X is selected from CH, C(CH_3) and N; and

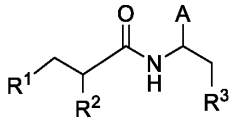
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

33. The compound is represented by:



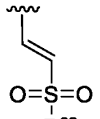
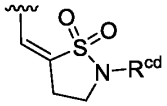
Formula II-A.

34. The compound is represented by:



Formula II-B.

35. A is selected from the group consisting of cyano, –C(O)R^D, –C(O)CH_2N($R^b$$R^c$), –C(O)$CH_2$OC(O)$R^D$, –C(O)C(O)$R^D$, –(CH=CH)C(O)O$R^D$, –(CH=CCN)C(O)O$R^D$, –

(CH=CCN)C(O)(NH)R^D, –CH(CN)(OH), -CH(CN)(NR^{b}R^c),  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, -OR^{bb} – N(R^bR^c), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

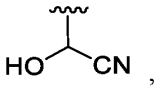
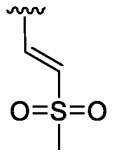
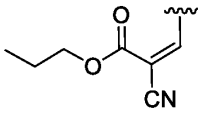
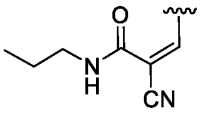
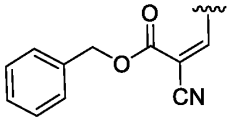
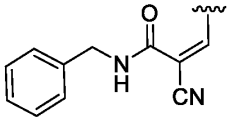
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy and C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

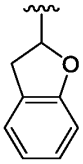
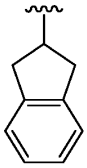
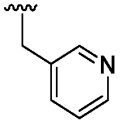
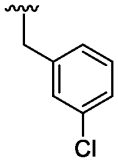
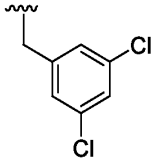
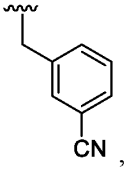
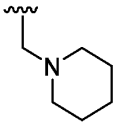
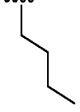
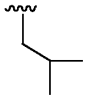
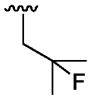
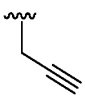
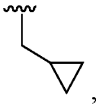
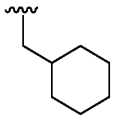
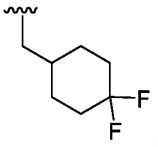
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

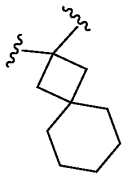
R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

36. A is selected from the group consisting of -CN,  ,  ,  ,  ,  , and  .

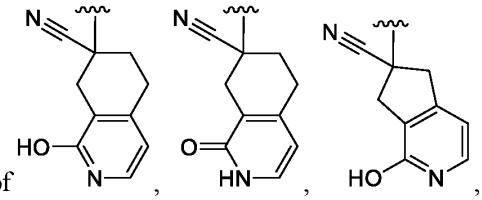
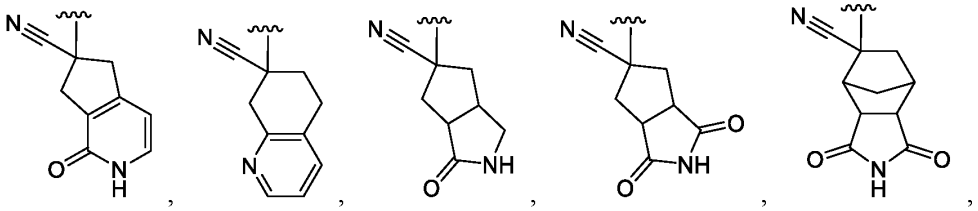
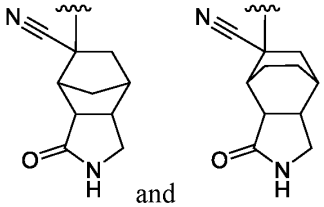
37. R^{1a} is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

38. R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

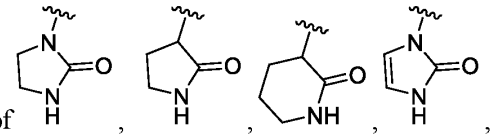
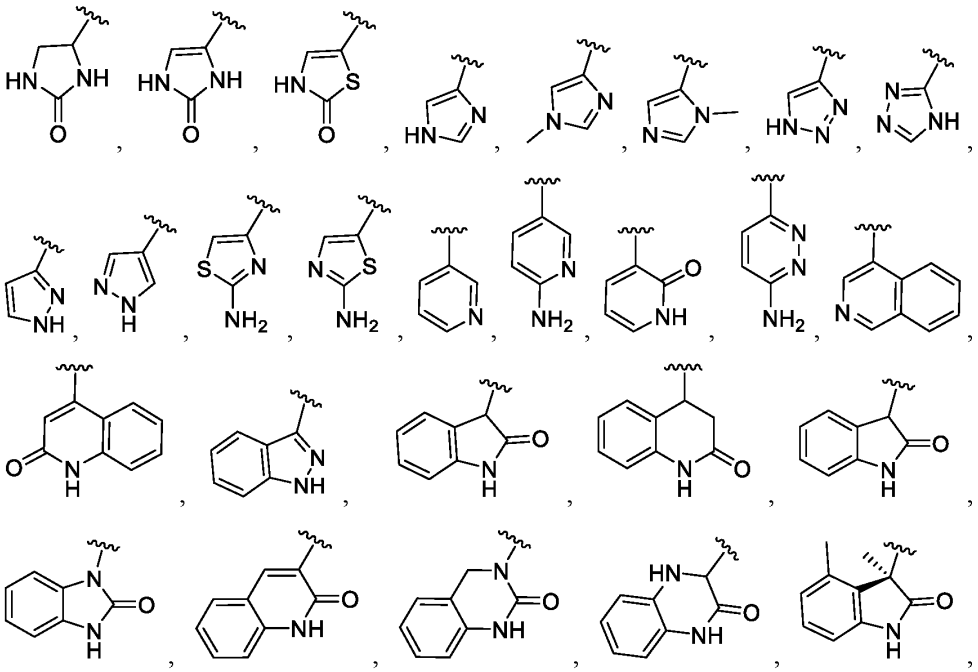
39. R^{1b} is hydrogen.

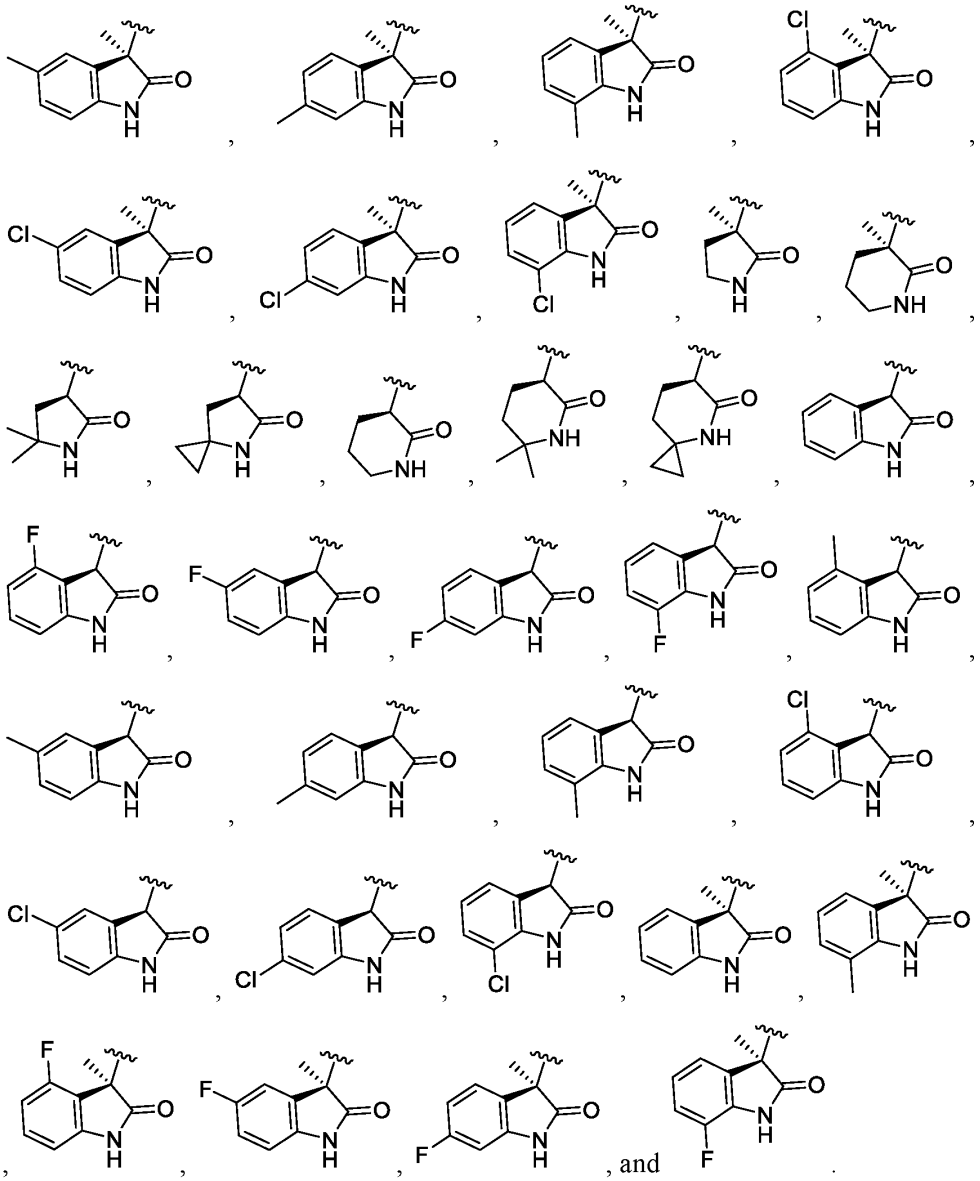
40. R^{1a} and R^{1b} are joined to together to form  .

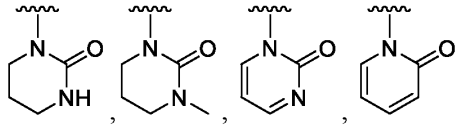
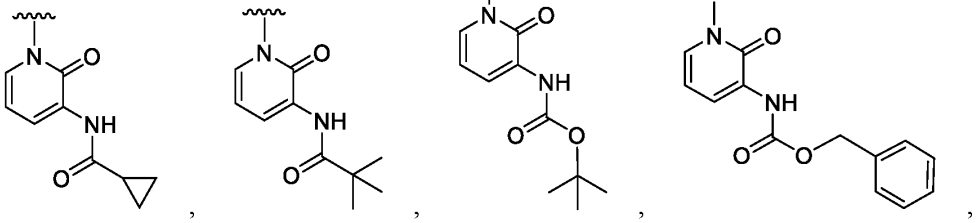
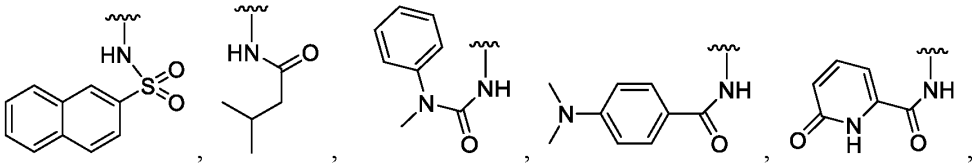
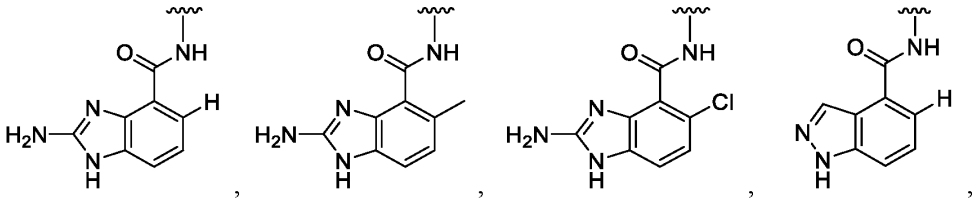
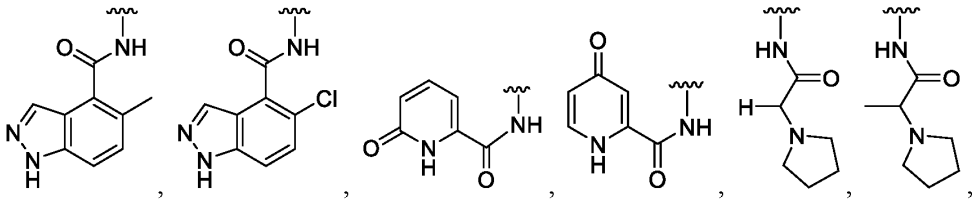
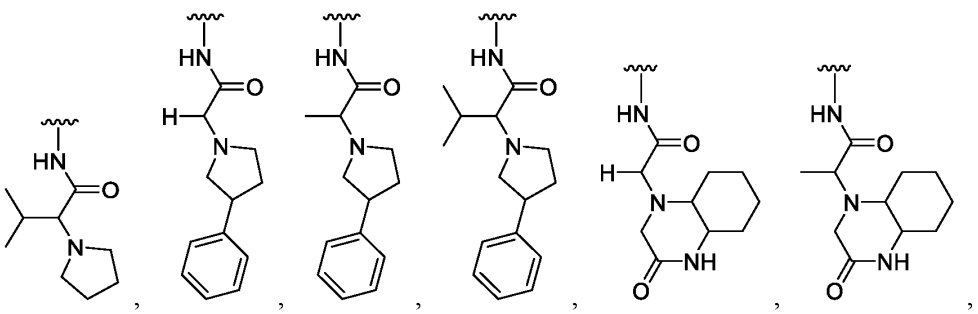
41. R^{3a} is a 4-10 membered heterocycle substituted by A.

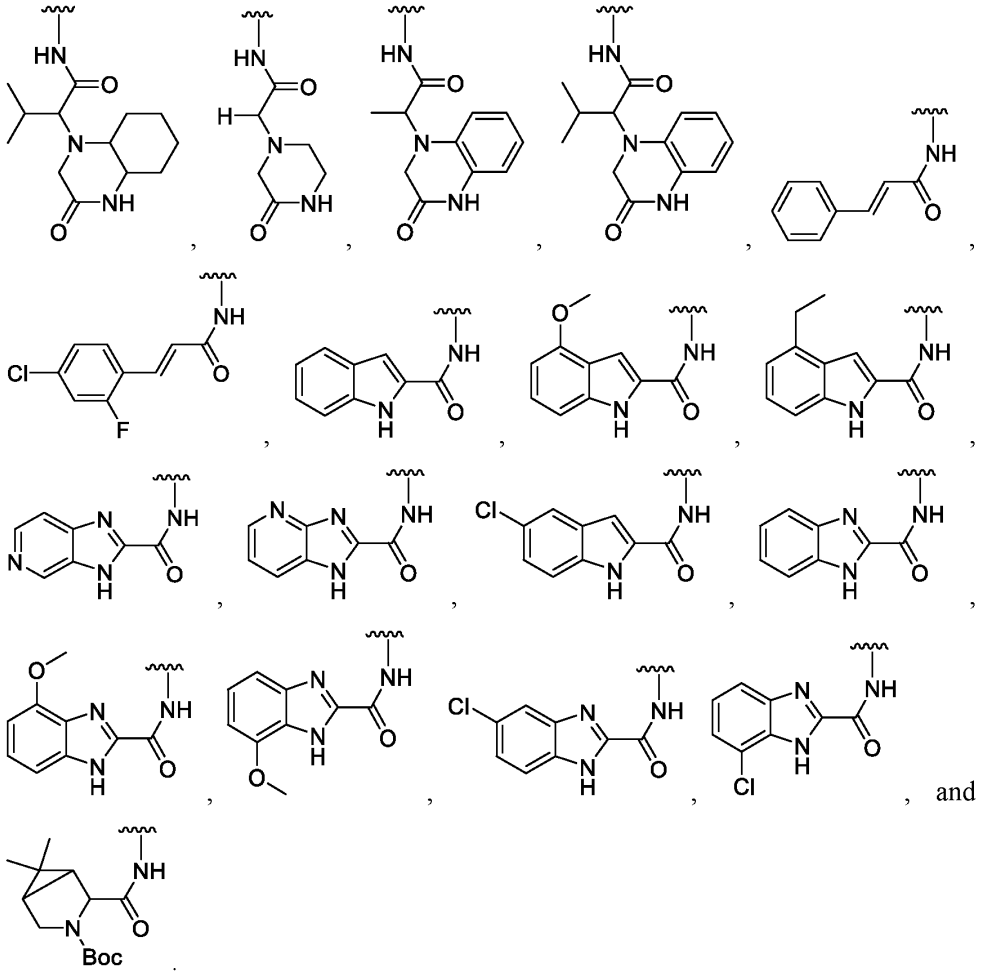
42. R^{3a} is selected from the group consisting of  ,  ,  and .

43. R^3 is a 4-10 membered heterocycle.

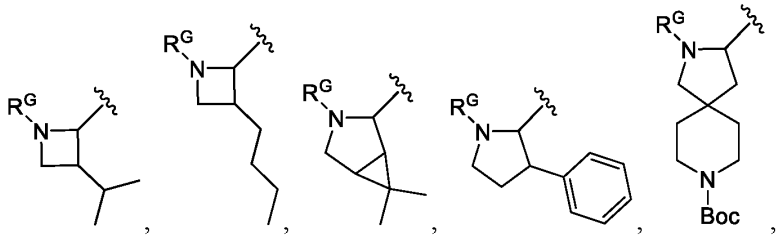
44. R^3 is selected from the group consisting of  , 

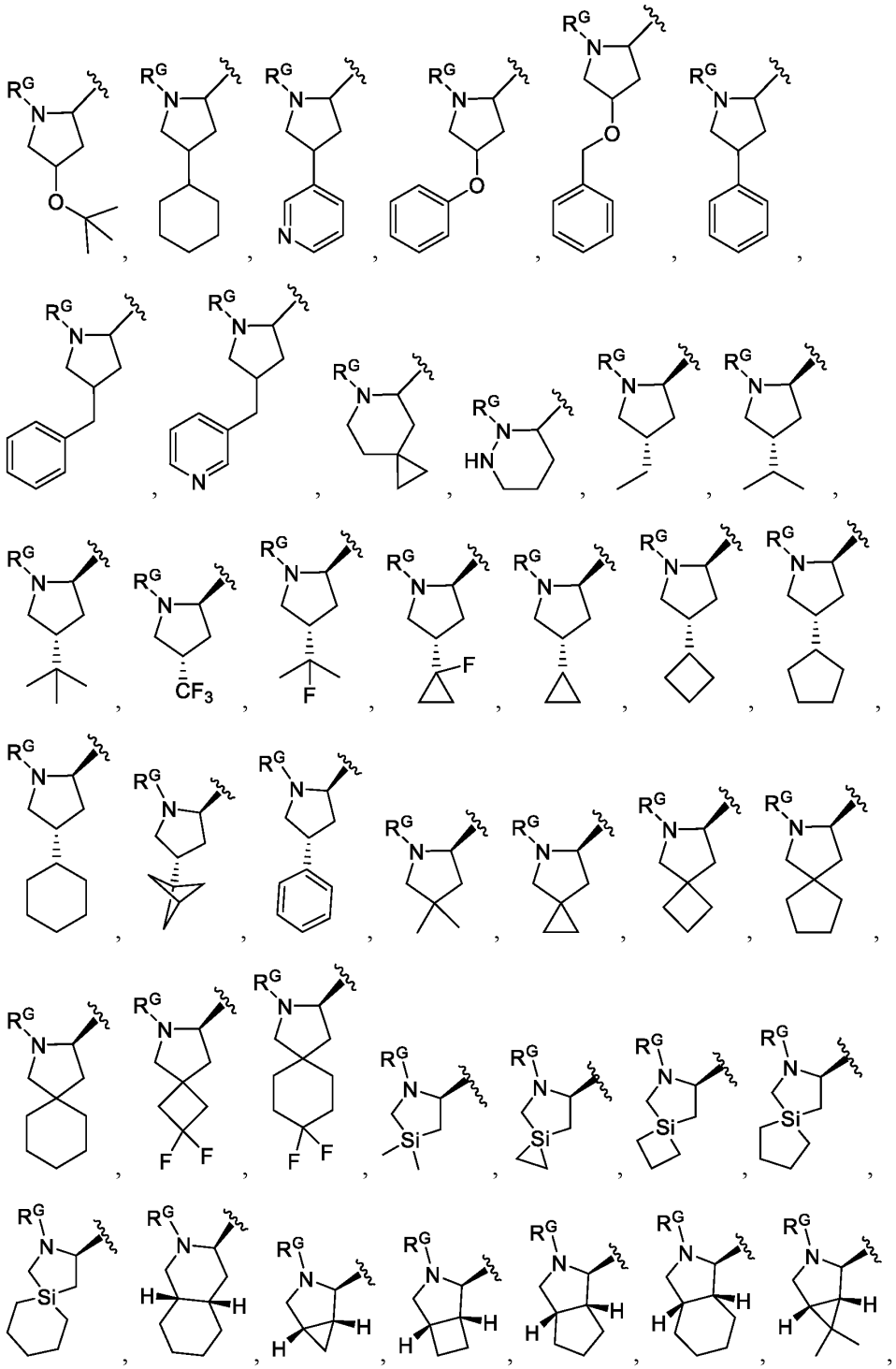


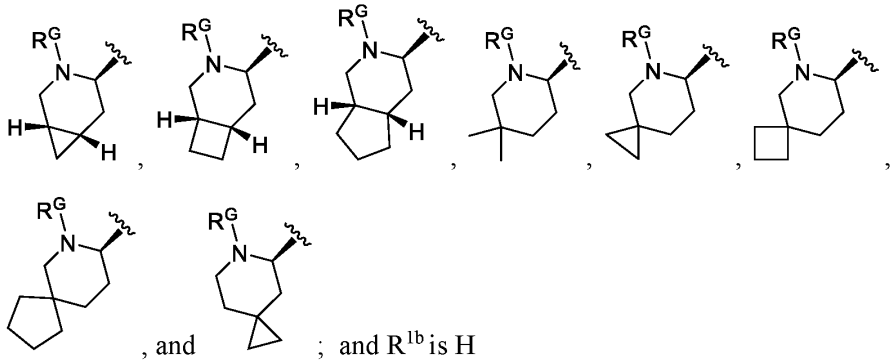
45. R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  .



46. R^{1a} and R^2 are joined to together to form the heterocycle selected from the group consisting of:

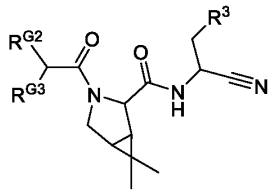






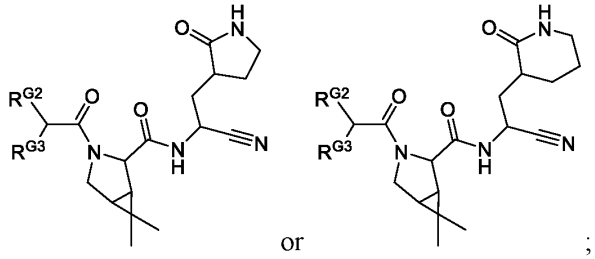
, and ; and R^{1b} is H

48. The compound is represented by:

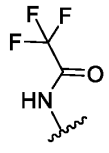


, wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, methyl or CF_3.

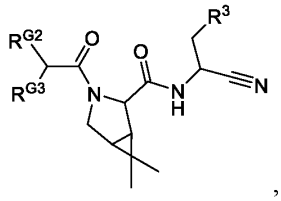
49. The compound is represented by:



or ;

wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, methyl or CF_3, e.g., R^{G2} is  .

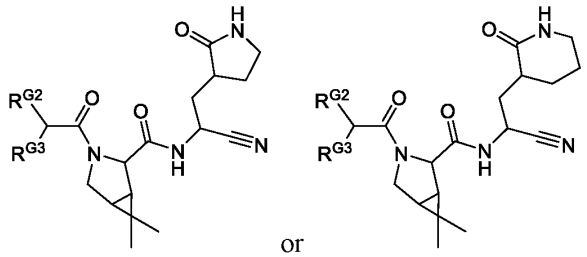
50. The compound is represented by:



,

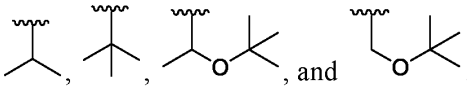
wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three C_1-C_6alkoxy), C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is selected from the group consisting of -NH(C_{1-3}alkyl) (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, optionally substituted phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl) and -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), CHF_2, CF_3, or 5-6 membered heteroaryl (optionally substituted by halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, CHF_2, and CF_3).

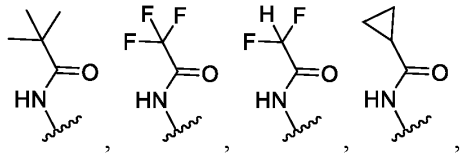
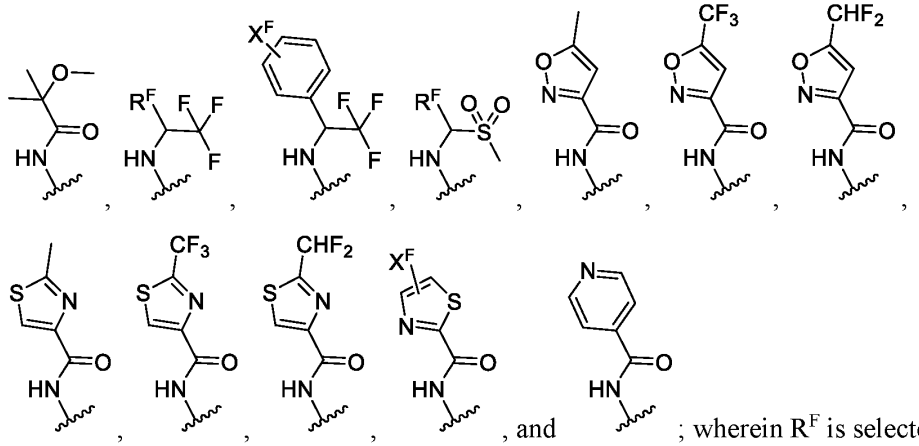
51. The compound is represented by:



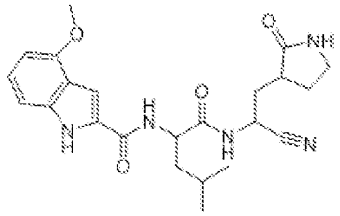
or

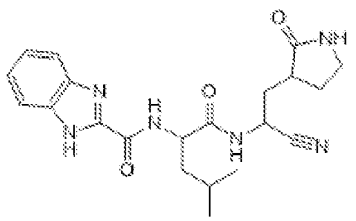
wherein R^{G3} is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three C_1-C_6alkoxy), C_{3-6}cycloalkyl, phenyl and heterocycle; and R^{G2} is selected from the group consisting of -NH(C_{1-3}alkyl) (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, optionally substituted phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl) and -NH(C=O)R^m, wherein R^m is selected for each occurrence by H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), CHF_2, CF_3, or 5-6 membered heteroaryl (optionally substituted by halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, CHF_2, and CF_3).

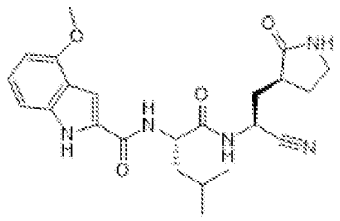
52. R^{G3} is selected from the group consisting of  .

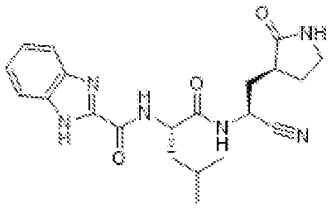
53. R^{G2} is selected from the group consisting of  ,  ; wherein R^F is selected from the group consisting of C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl and 5-6 membered heteroaryl, wherein R^F may optionally be substituted by one, two or three substituents selected from the group consisting of halo, cyano, hydroxyl and C_1-C_6alkoxy; and X^F is selected from the group consisting of H, halo, cyano, hydroxyl, NH_2, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_1-C_6alkoxy, and C_{1-6}haloalkyl.

54. The compound is selected from the group consisting of:

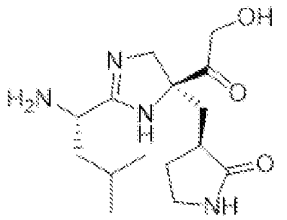
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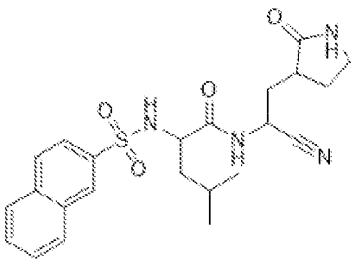
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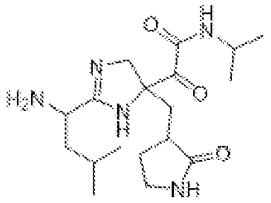
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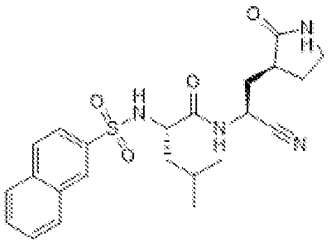
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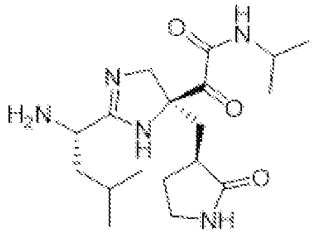
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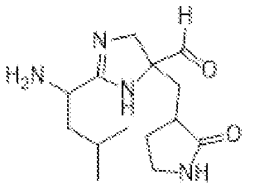
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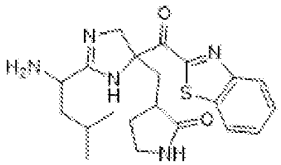
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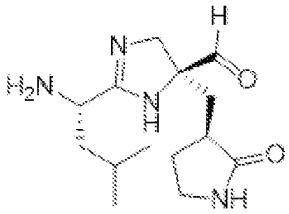
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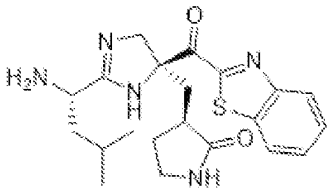
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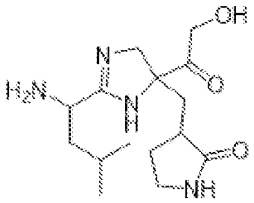
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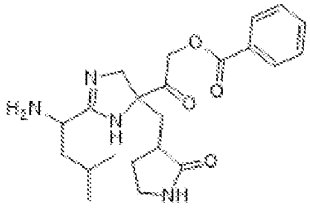
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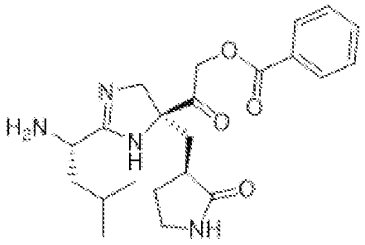
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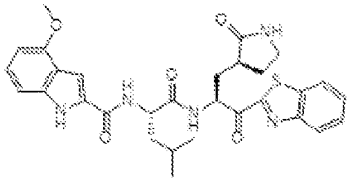
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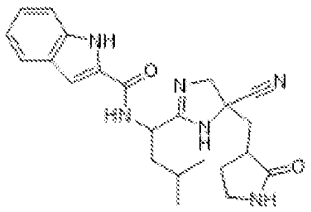
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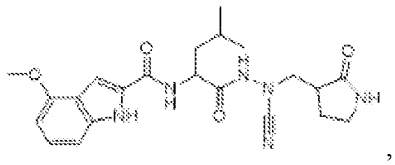
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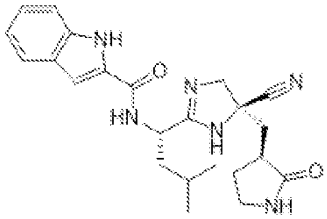
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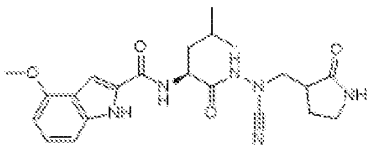
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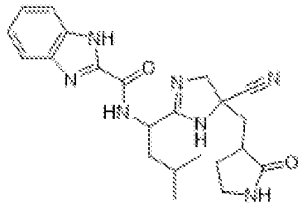
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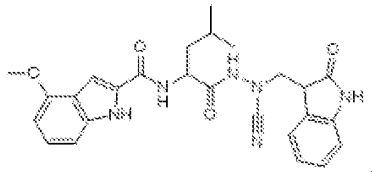
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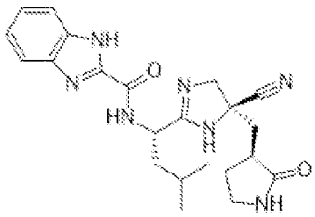
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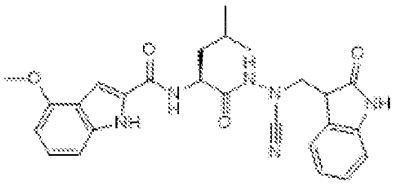
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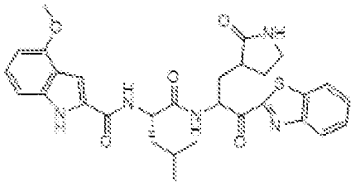
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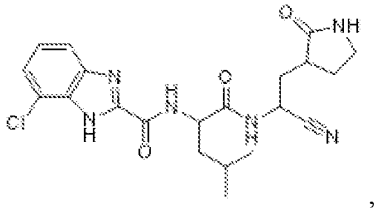
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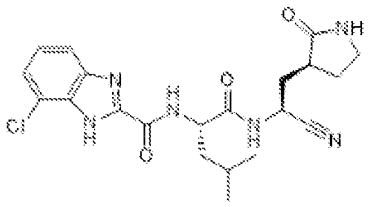
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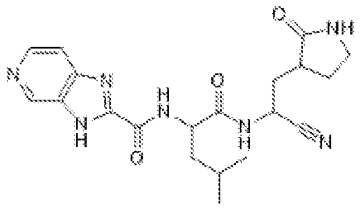
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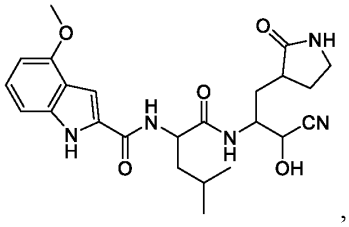
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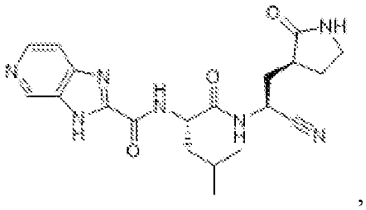
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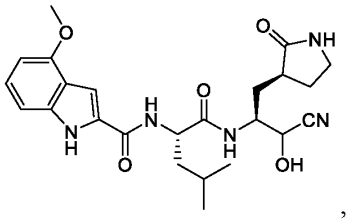
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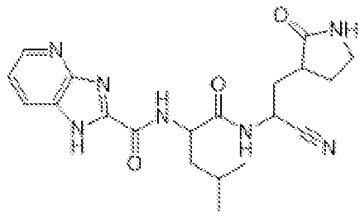
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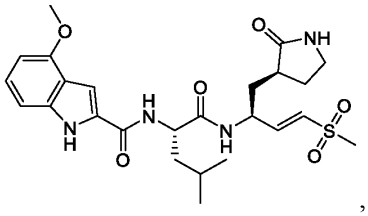
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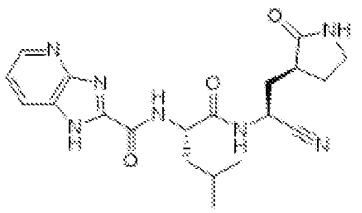
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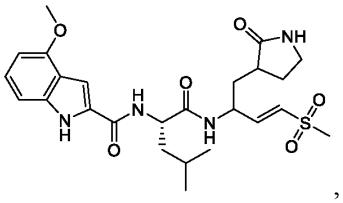
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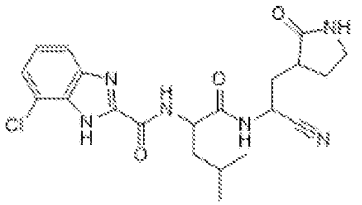
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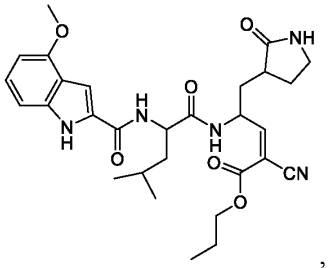
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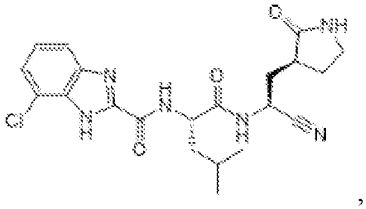
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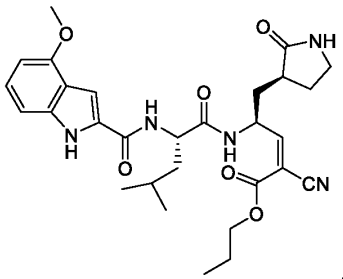
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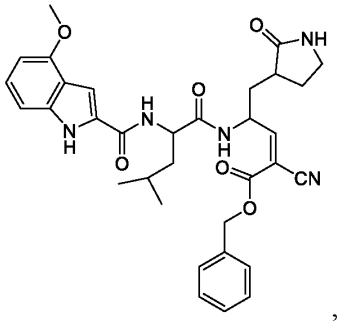
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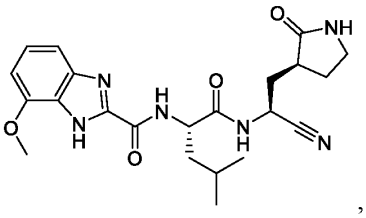
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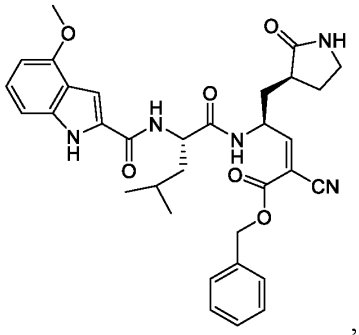
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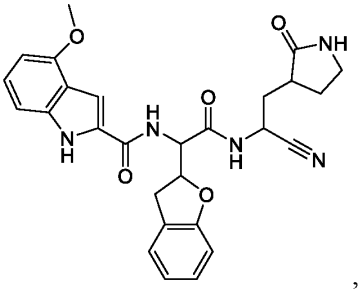
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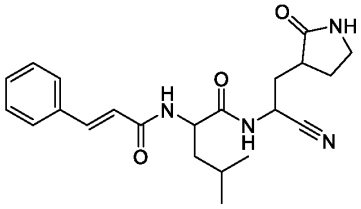
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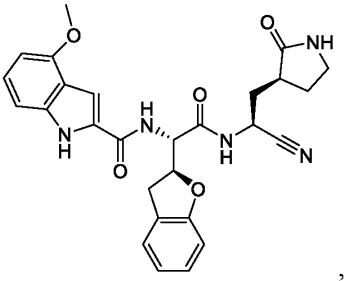
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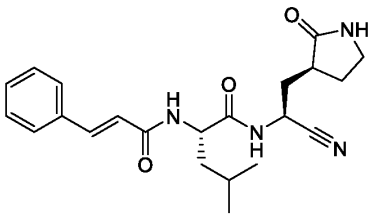
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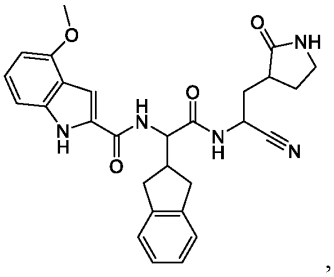
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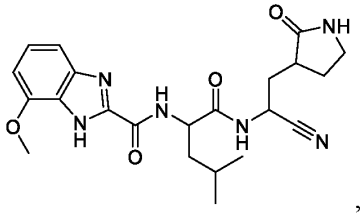
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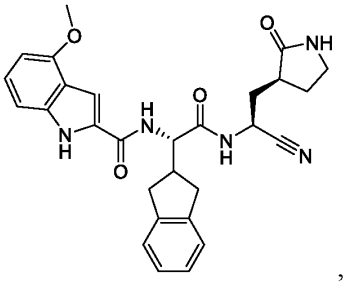
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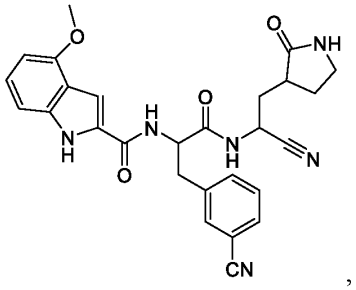
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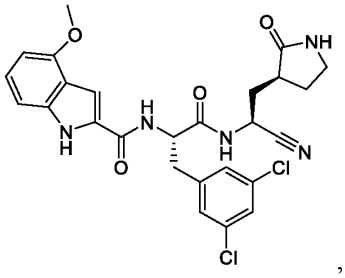
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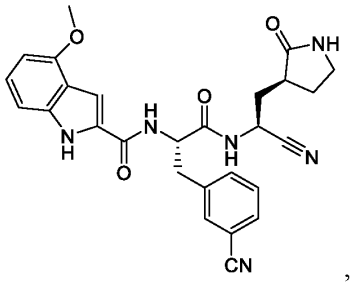
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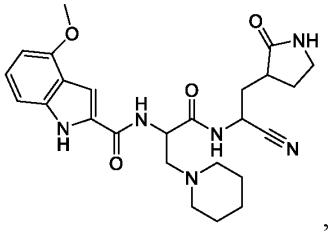
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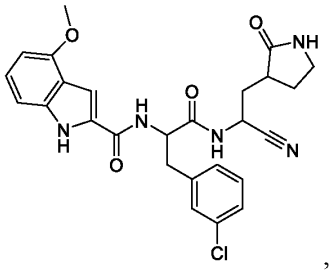
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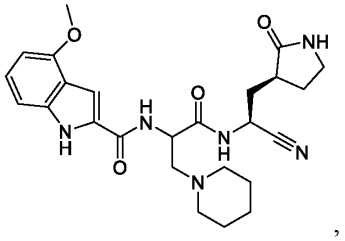
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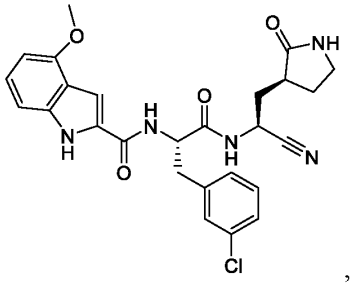
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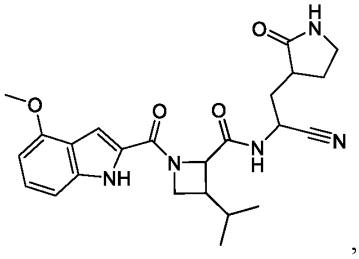
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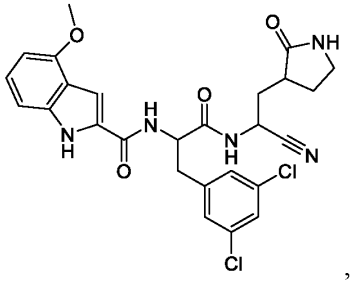
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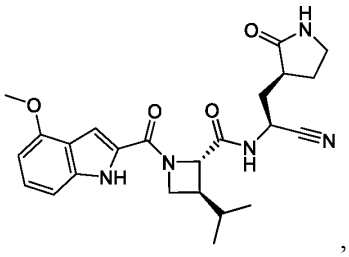
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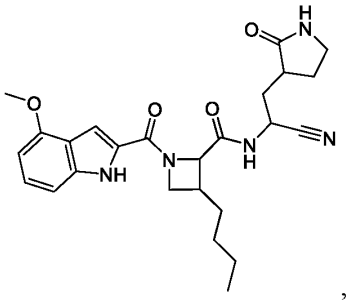
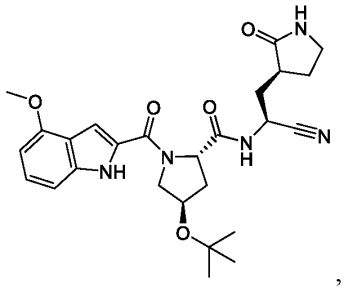
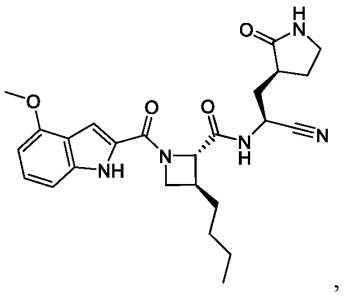
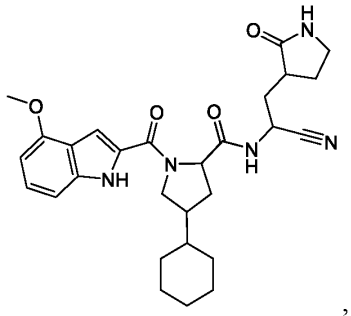
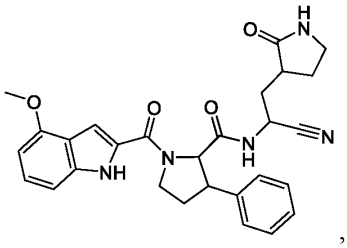
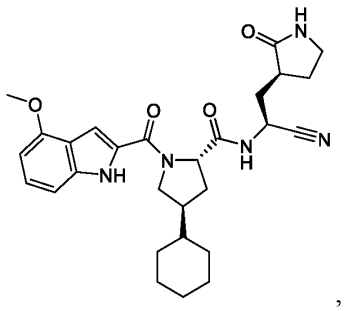
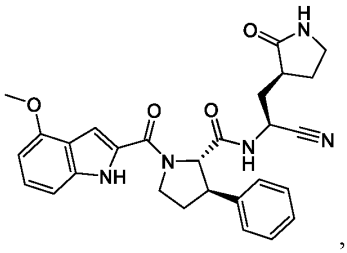
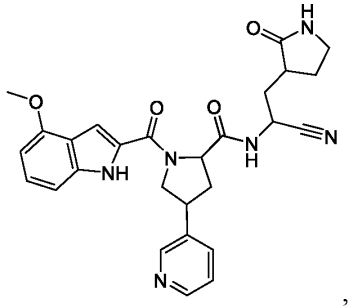
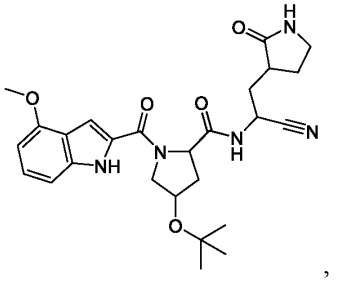
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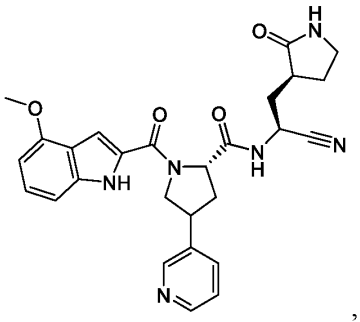


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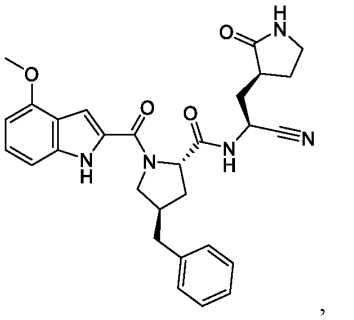


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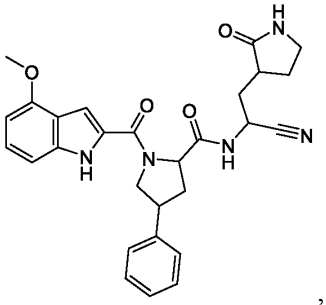

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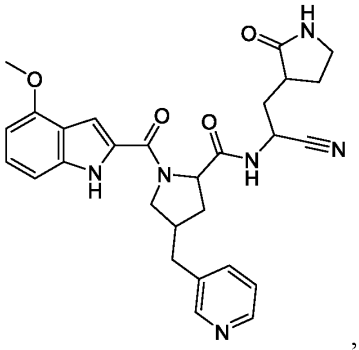
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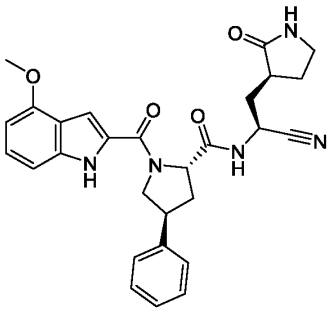
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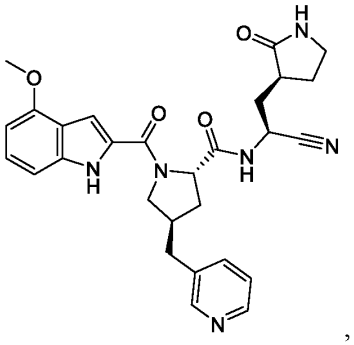
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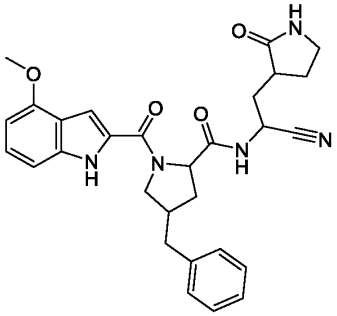
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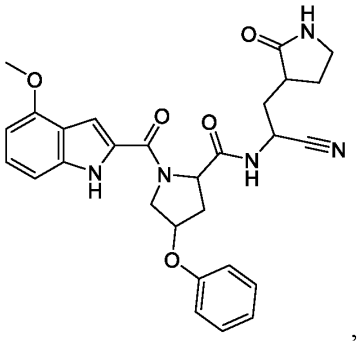
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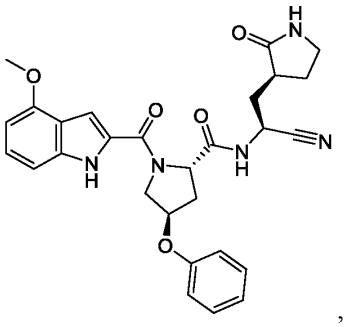
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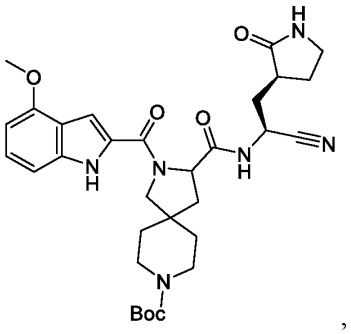
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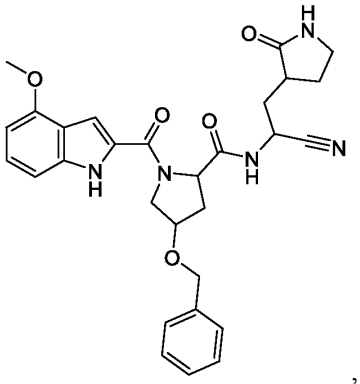
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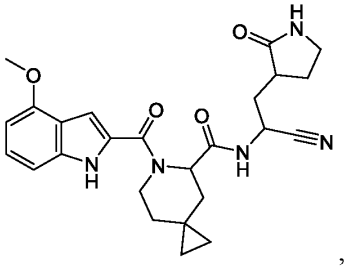
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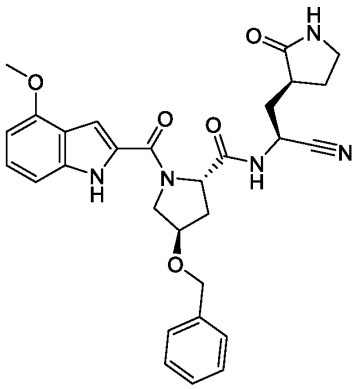
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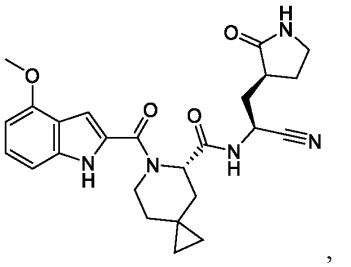
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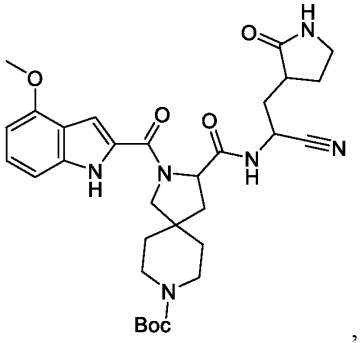
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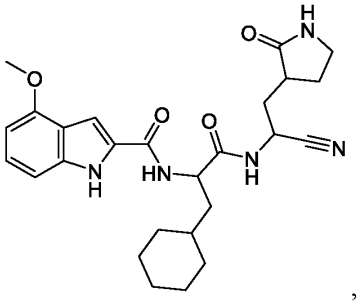
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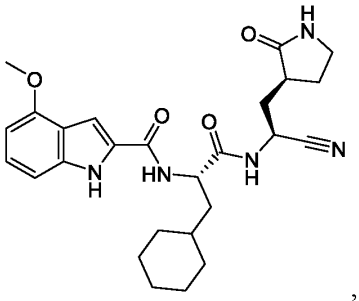
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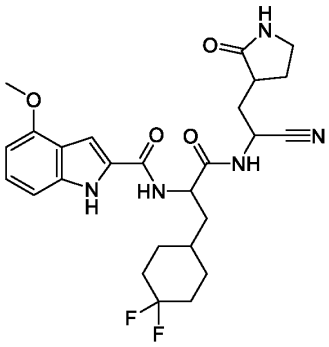
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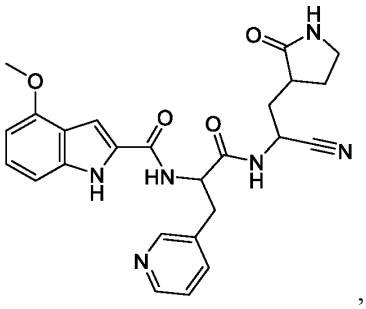
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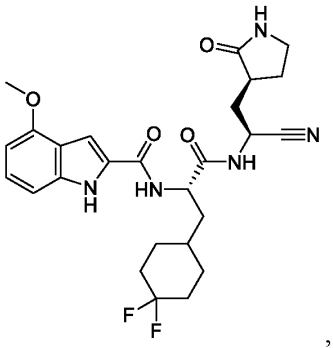
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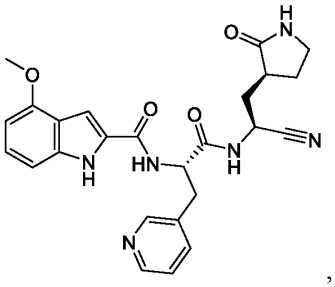
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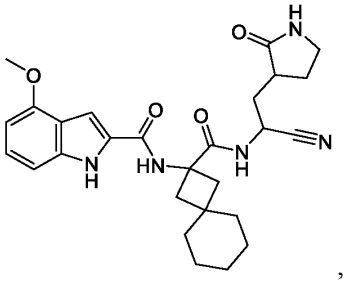
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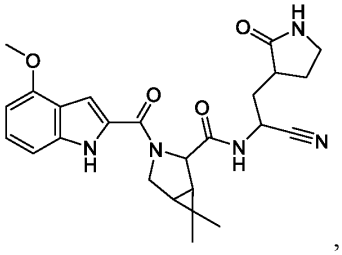
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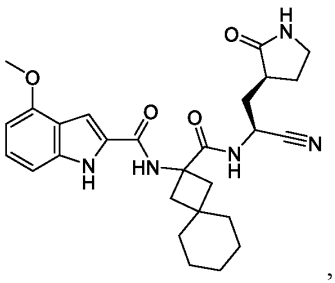
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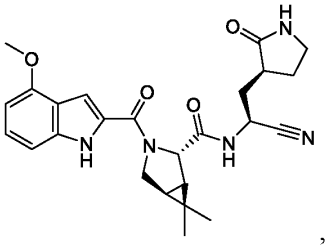
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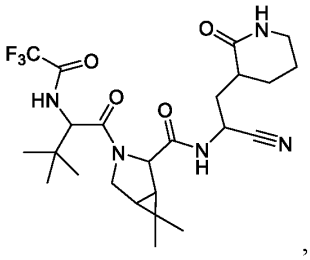
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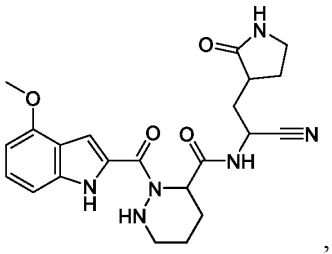
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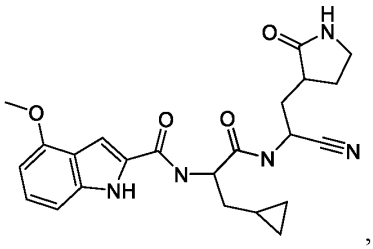
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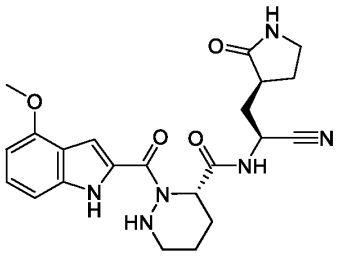
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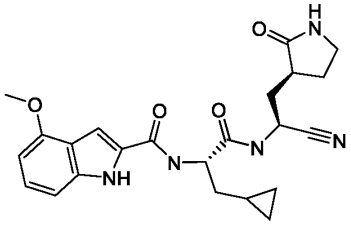
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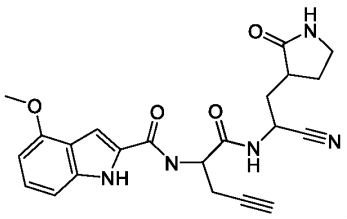
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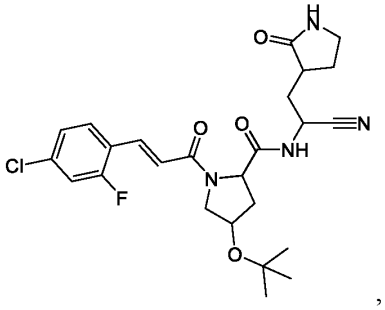
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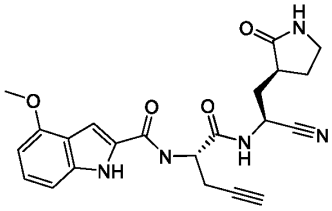
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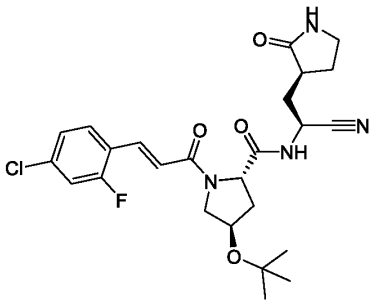
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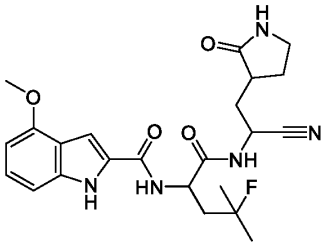
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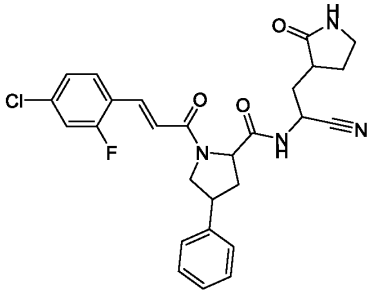
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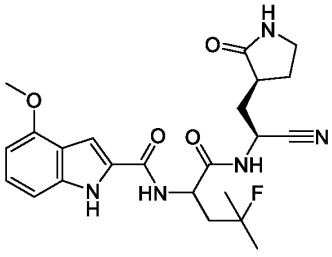
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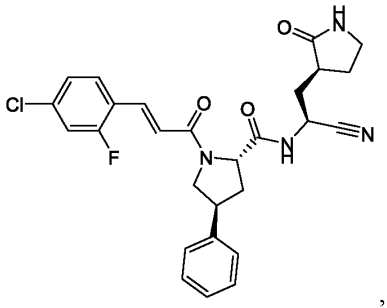
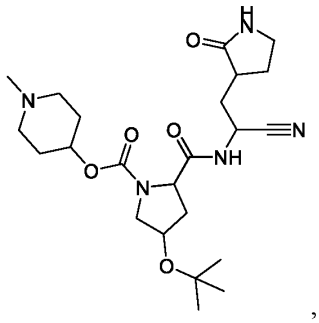
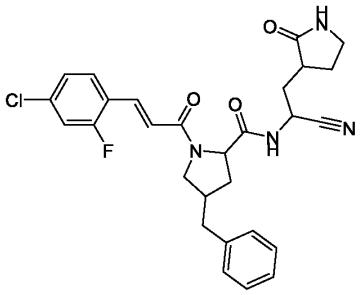
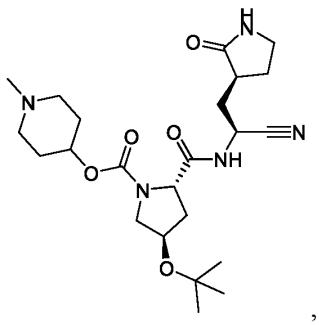
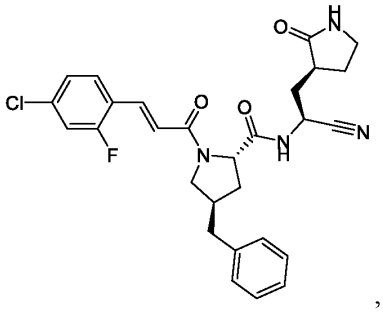
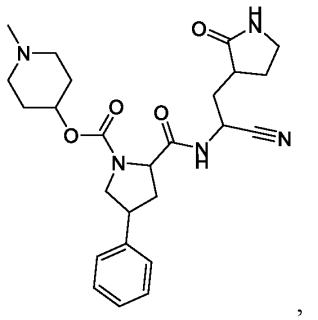
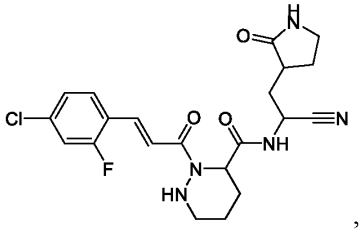
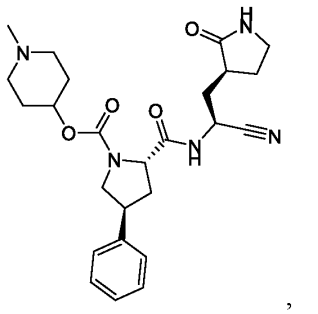
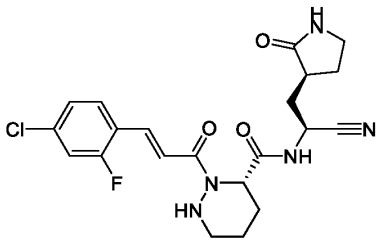
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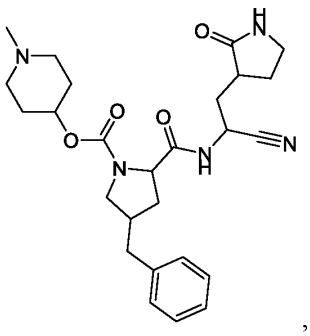


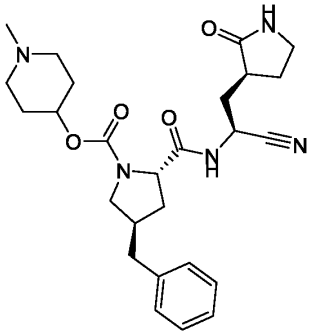
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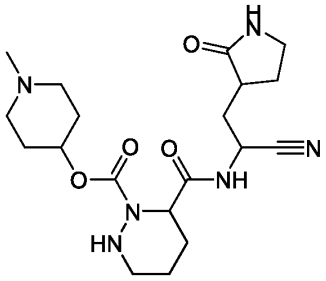


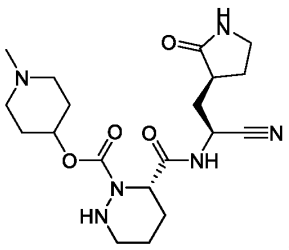
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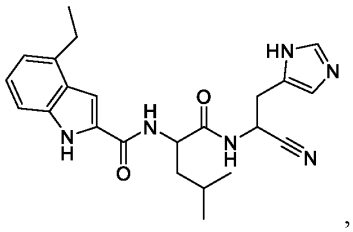

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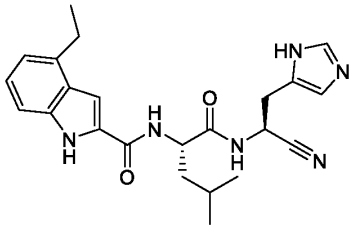

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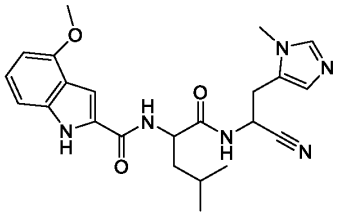

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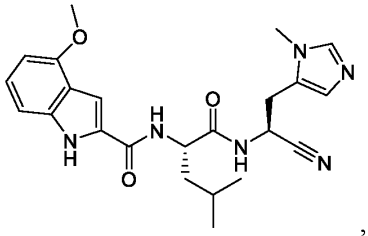

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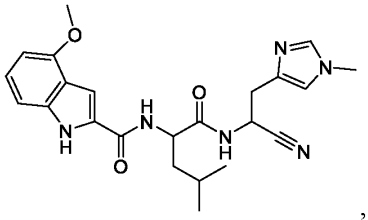

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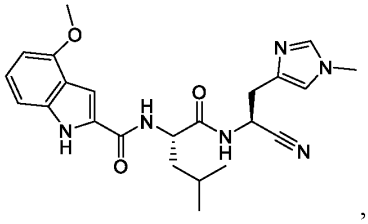

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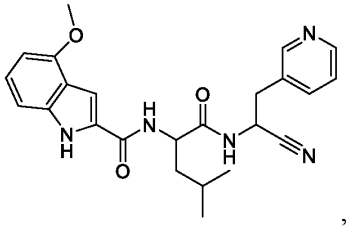

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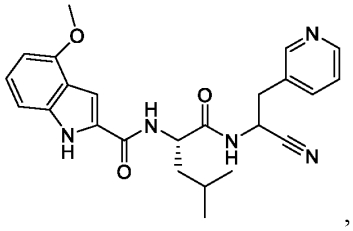

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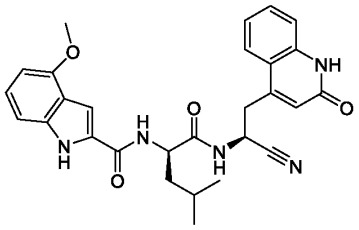

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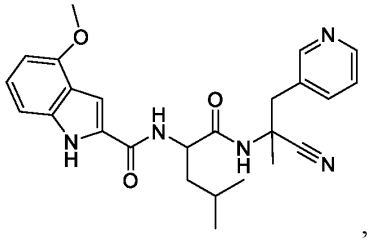

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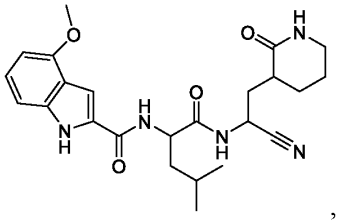
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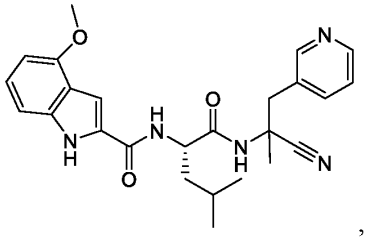
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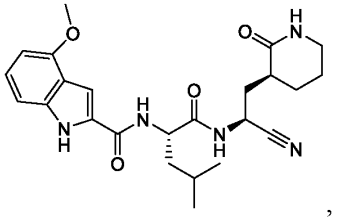
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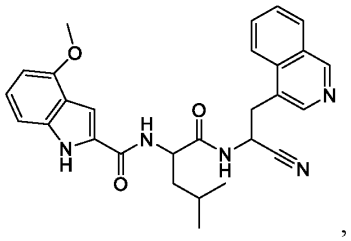
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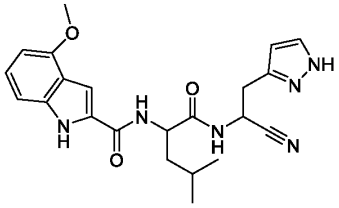
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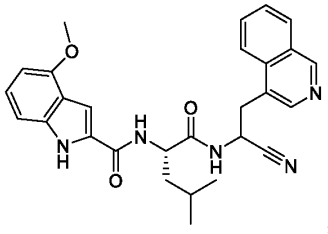
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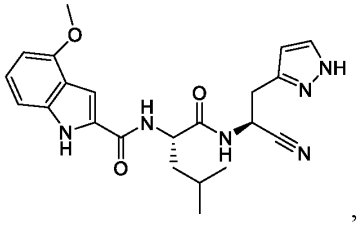
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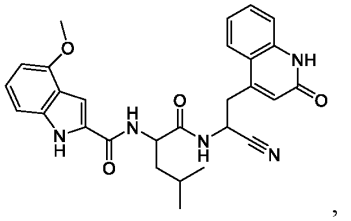
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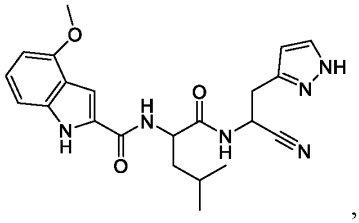
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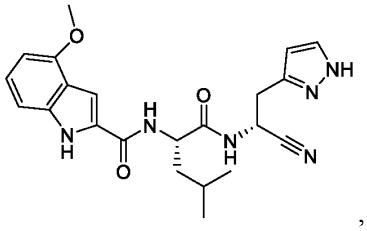
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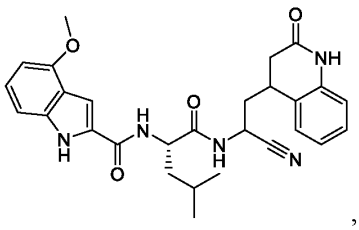
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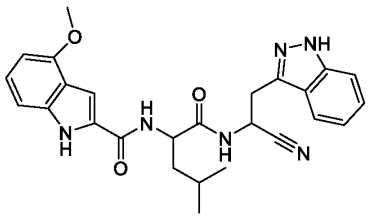
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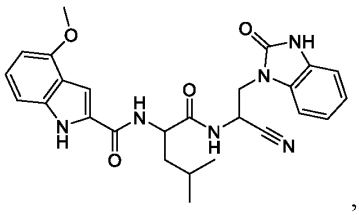
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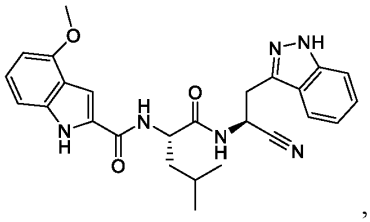
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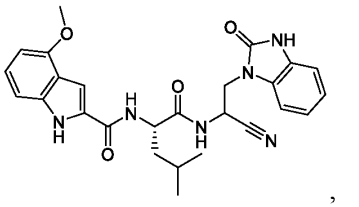
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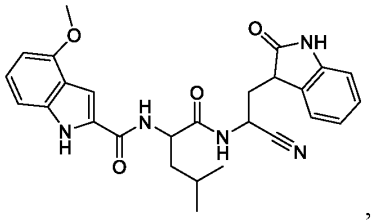
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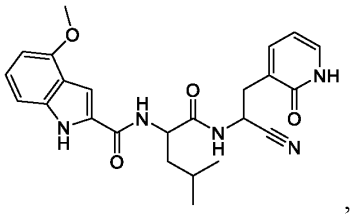
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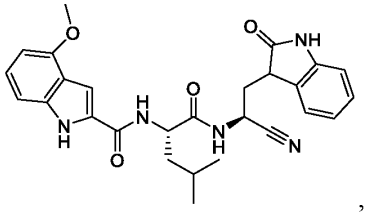
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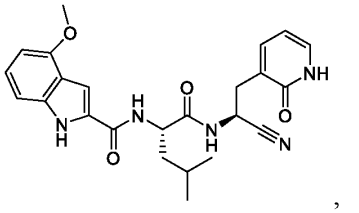
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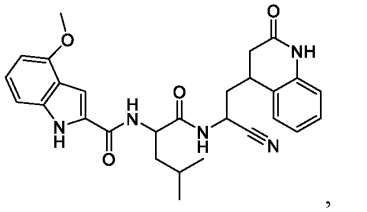
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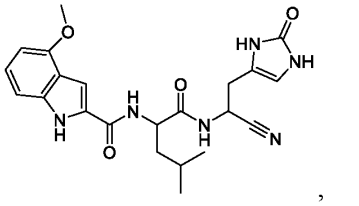
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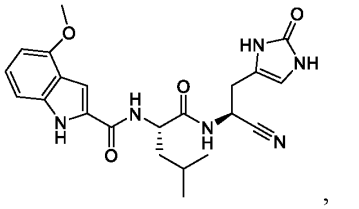


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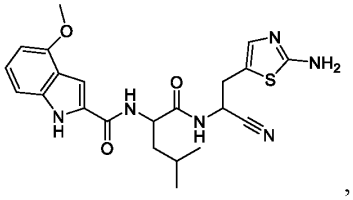


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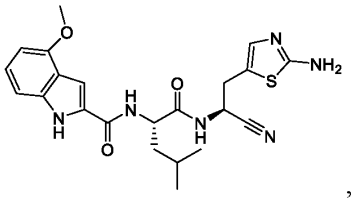
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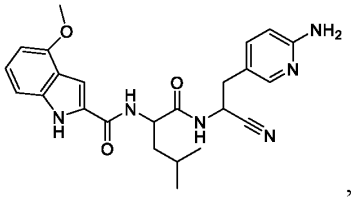
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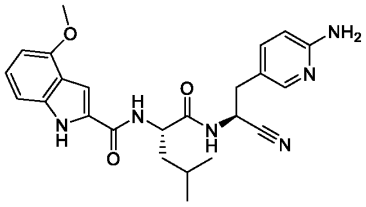
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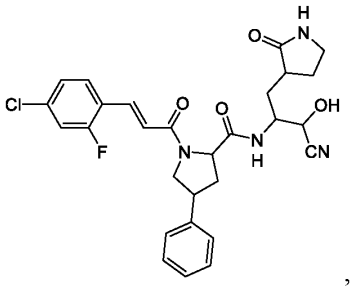
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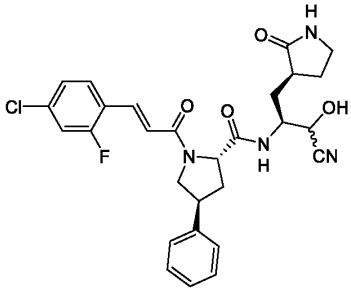
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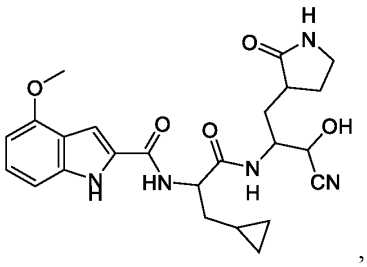
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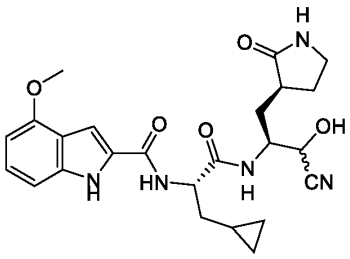
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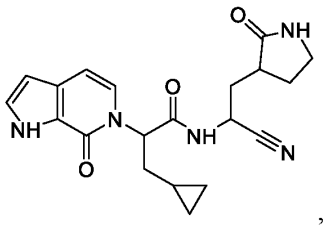
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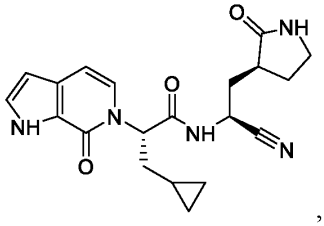
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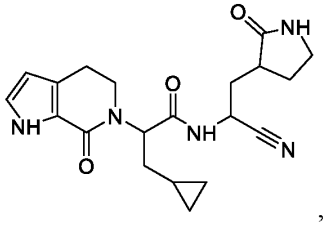
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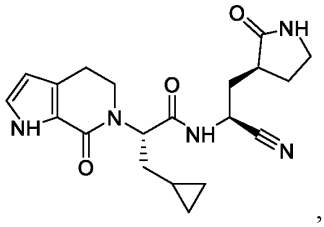
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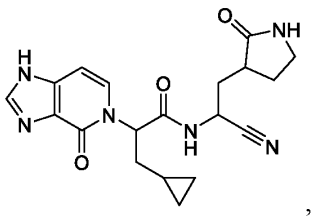
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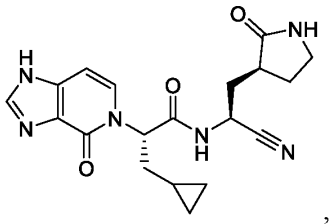
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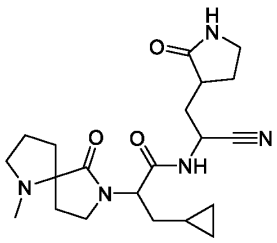
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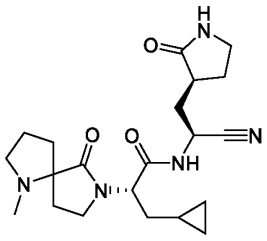
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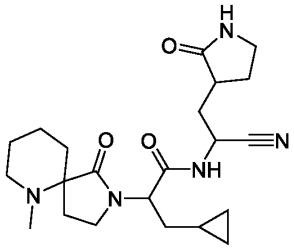
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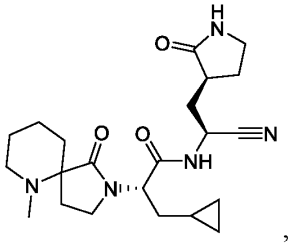
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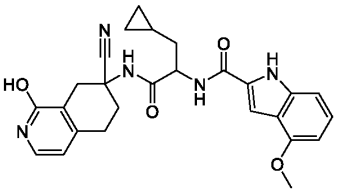
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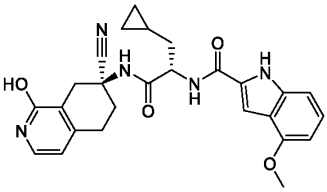
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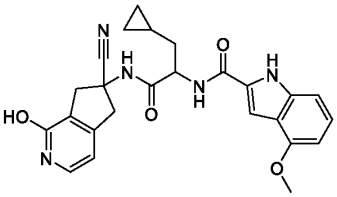
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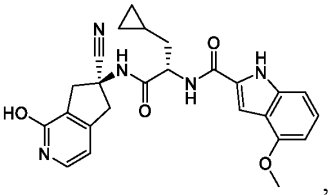
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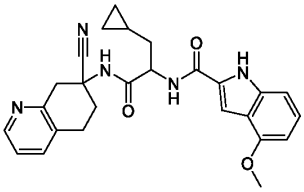
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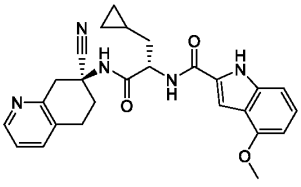
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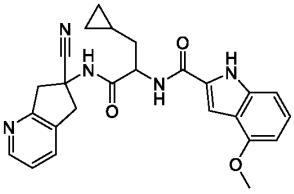
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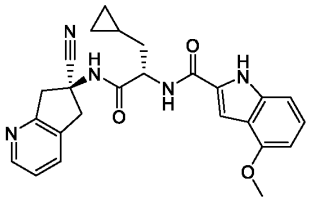
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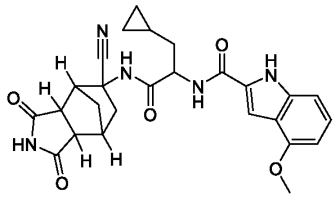
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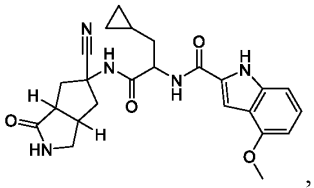
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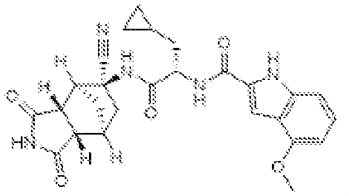
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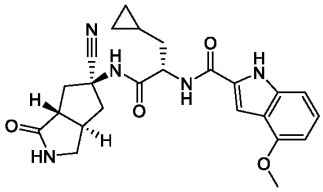
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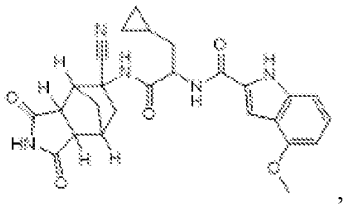
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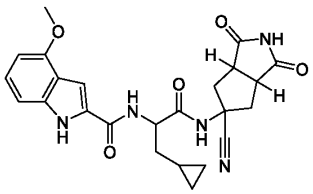
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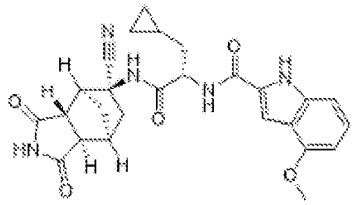
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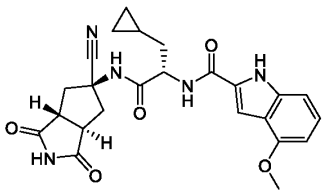
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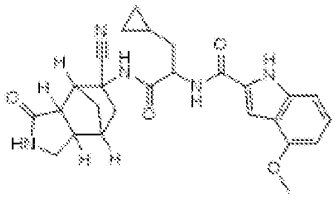
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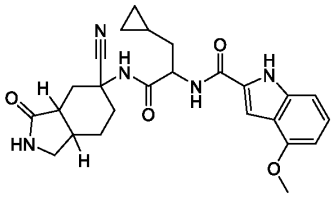
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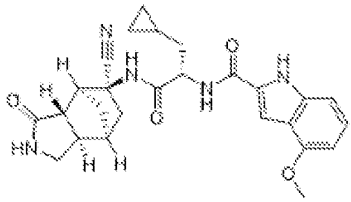
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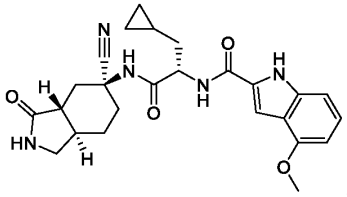
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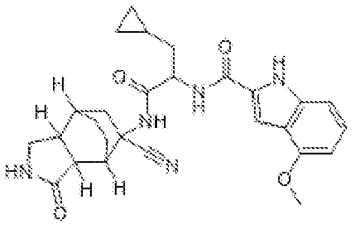
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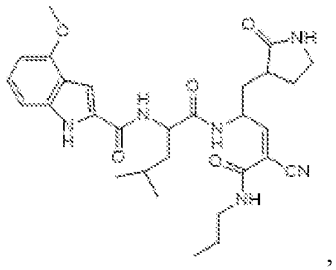
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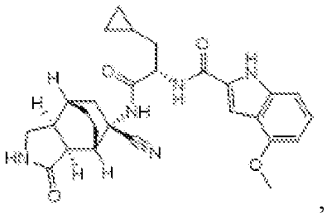
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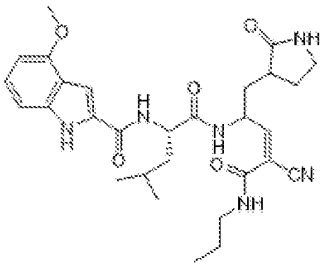
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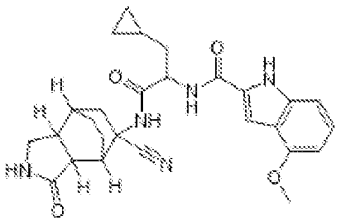
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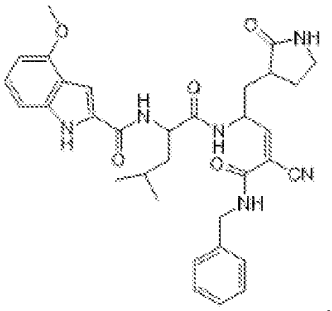
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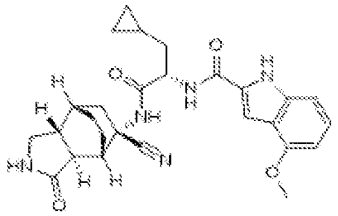
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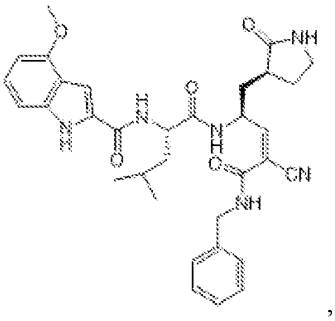
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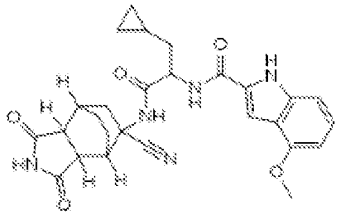
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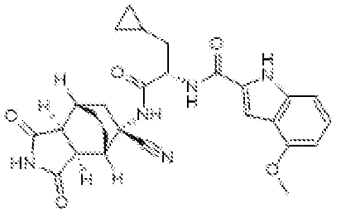
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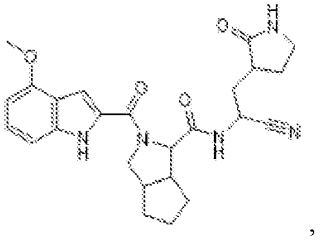
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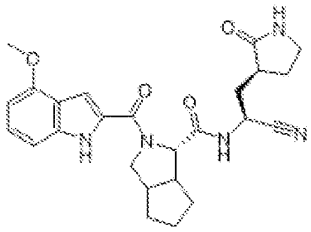
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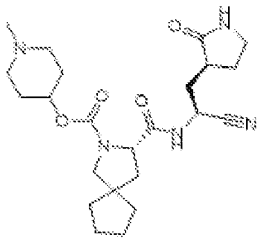


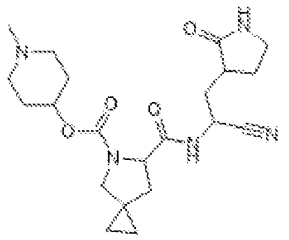
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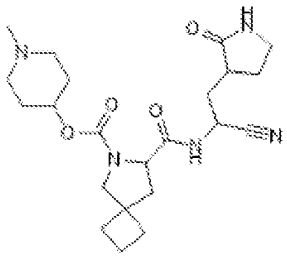


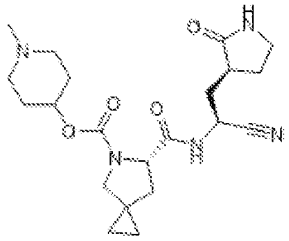
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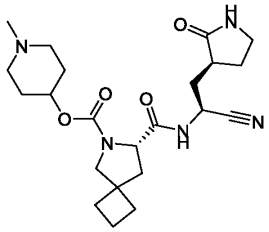

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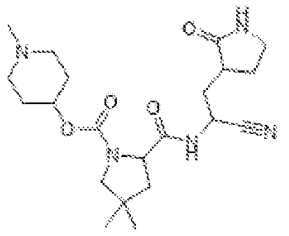

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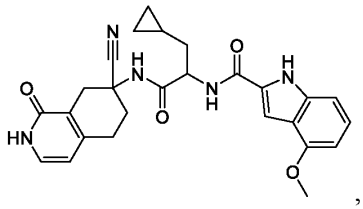

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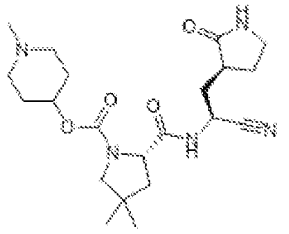

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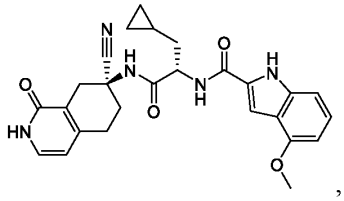

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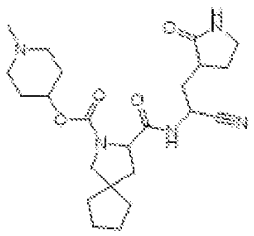

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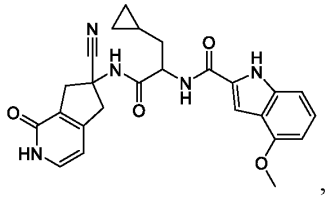

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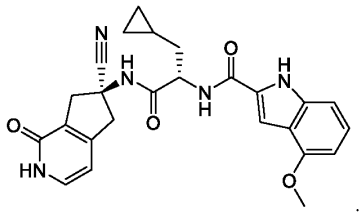

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55. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds of the embodiment.

56. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
57. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.
58. The viral infection is a coronavirus infection.
59. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).
60. The viral infection is SARS-CoV-2.
61. The viral infection is an arenavirus infection.
62. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.

63. The viral infection is an influenza infection.

64. The influenza is influenza H1N1, H3N2 or H5N1.

65. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of any compound of the embodiment to a patient suffering from the virus, and/or contacting an effective amount of any compound of the embodiment with a virally infected cell.

66. The method further comprises administering another therapeutic.

67. The method further comprises administering an additional anti-viral therapeutic.

68. The anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, and remdesivir.

69. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

70. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, and remdesivir.

71. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of any compound of the embodiment,

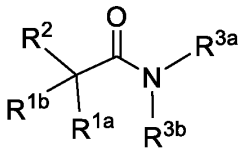
72. The compound is administered before viral exposure.

73. The compound is administered after viral exposure.

9. Contemplated Embodiment

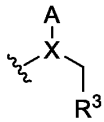
[000198] In another aspect, the compositions, compounds and methods of the present disclosure may be described in another embodiment as follows:

1. A protease inhibitor compound represented by:



Formula II,

wherein:



R^{3a} is selected from and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen, NR^G, or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10

membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected, for each occurrence, halogen, cyano, hydroxyl, oxo, SF_5, $–CH_2CF_3$, CF_3, $–O-CF_3$, $–O-CHF_2$, $–S-CH_3$, $–S(O)_2-CH_3$, $–NH_2$, –O-phenyl, $–O-(C_1-C_8alkyl)$-phenyl, $–NHC(O)R^B$, $–NHC(O)OR^B$, $–NHC(O)O-(C_1-C_8alkyl)-R^B$, $–N(R^y)_2$, $–N(R^y)(C_1-C_8alkyl)C(O)O$-phenyl, $–N(R^y)(C_1-C_8alkyl)C(O)N(R^y)_2$, $–NHC(O)O(C_1-C_8alkyl)R^B$, –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocycle), –C(O)-O-(4-10 membered heterocycle), –C(O)-(4-10 membered heterocyclyloxy), $–C(O)-OC(CH_3)_3$, $–C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl)$, C_1-C_8alkyl, $C_2-C_{10}alkenyl$, $C_2-C_{10}alkynyl$, $C_1-C_8heteroalkyl$, $C_1-C_8alkoxy$, $C_3-C_{10}cycloalkyl$, $–(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, $–(C_1-C_8alkyl)-(C_6-C_{14}aryl)$, $–(C_1-C_8alkyl)$-(5-10 membered heteroaryl), $C_6-C_{14}aryl$, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the R^B, alkyl, heterocycle, heteroaryl, or aryl may optionally be substituted by one, two or three substituents of halogen, C_1-C_8alkyl, $C_1-C_8alkoxy$, SF_5, $–NH_2$, hydroxyl or oxo;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, $–O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, 4-10 membered heterocycle, $C_6-C_{14}aryl$ and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered mono or bicyclic heterocycle having a ring nitrogen NR^G, or a $C_3-C_{10}cycloalkyl$, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each selected from oxo, halogen and C_1-C_8alkyl;

R^G is selected from the group consisting of H, $C_{1\text{-}6}$alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m), and C(=O)-$C_{1\text{-}6}$alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano, -NR^mR^m, -NR^m(C=O)R^m, phenyl, cycloalkyl, heterocycle, C_1-C_6alkoxy, wherein R^m is selected for each occurrence by H, $C_{1\text{-}3}$alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo), phenyl (optionally substituted by halo), -$S(O)_2$-CH_3, $C_{3\text{-}6}$cycloalkyl, and 5-6 membered heteroaryl), -C(=O)-$C_{1\text{-}6}$alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano and C_1-C_6alkoxy), C(=O)-$C_{3\text{-}6}$cycloalkyl, and C(=O)-(5-6 membered heteroaryl) (optionally substituted by halo, cyano, hydroxyl, NH_2, $C_{1\text{-}6}$alkyl, $C_{3\text{-}6}$cycloalkyl, C_1-C_6alkoxy, and $C_{1\text{-}6}$haloalkyl));

R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6;

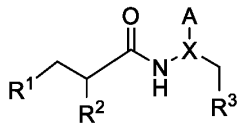
R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, $–CH_2CF_3$, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH;

A is a warhead;

X is selected from the group consisting of $C(R^{xy})$ and N, wherein R^{xy} is selected from the group consisting of H, D, -OH, $-NH_2$, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy; and

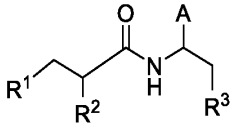
pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

2. The compound is represented by:



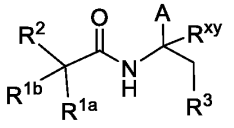
Formula II-A.

3. The compound is represented by:



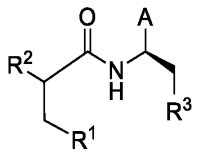
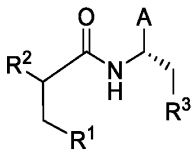
Formula II-B.

4. The compound is represented by:

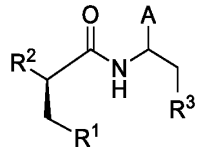
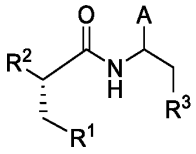


Formula II-C.

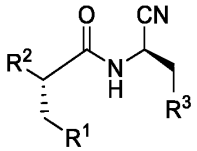
5. The compound is represented by:


(Formula II-D-A) or 
(Formula II-D-B).

6. The compound is represented by:

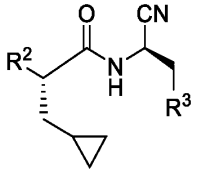

(Formula II-E-A) or 
(Formula II-E-B).

7. The compound is represented by:



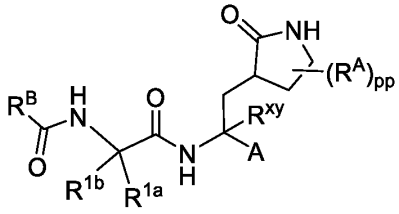
Formula II-F.

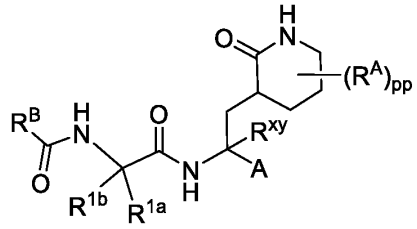
8. The compound is represented by:



Formula II-G.

9. The compound is represented by:

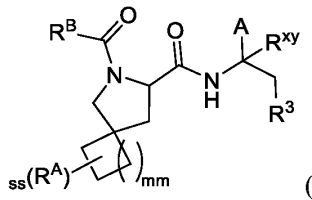

(Formula II-D-I), or



(Formula II-D-II),

wherein pp is selected from 0, 1, 2, and 3.

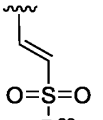
10. The compound is represented by:



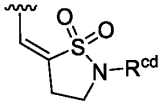
(Formula II-E),

wherein ss is selected from 0, 1, 2, and 3, and mm is selected from 1, 2, and 3.

11. A is selected from the group consisting of cyano, $-C(O)R^D$, $-C(O)CH_2N(R^bR^c)$, $-C(O)CH_2OC(O)R^D$, $-C(O)C(O)R^D$, $-(CH=CH)C(O)OR^D$, $-(CH=CCN)C(O)OR^D$, $-(CH=CCN)C(O)(NH)R^D$, $-CH(CN)(OH)$, $-CH(CN)(NR^bR^c)$,



, and



, wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, $-OR^{bb}$, $-N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted by one, two, or three substituents each selected from the group consisting of halogen, hydroxyl, and R^E;

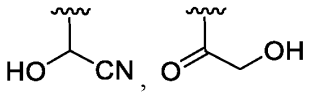
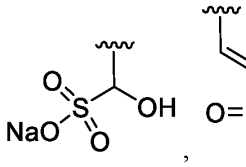
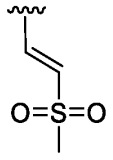
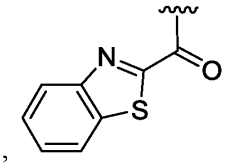
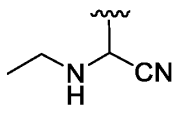
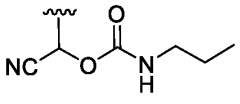
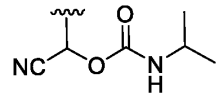
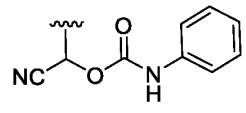
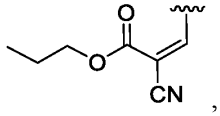
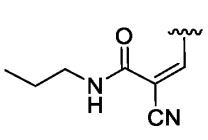
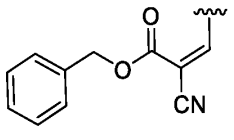
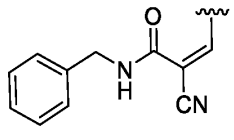
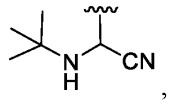
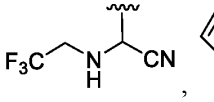
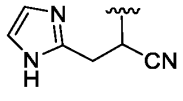
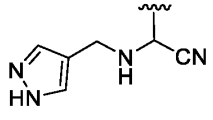
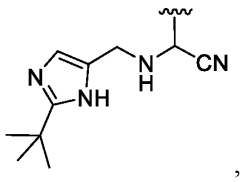
R^E is selected from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each selected from halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

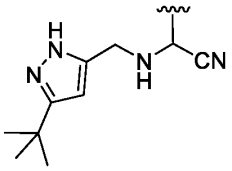
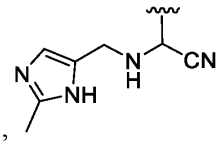
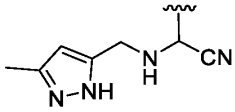
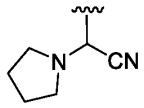
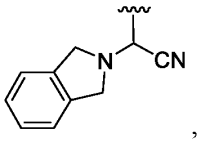
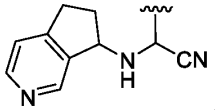
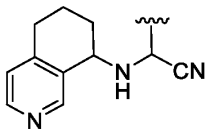
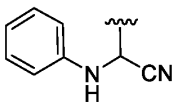
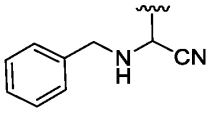
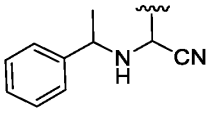
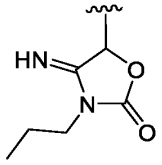
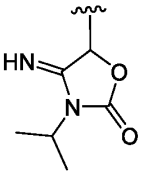
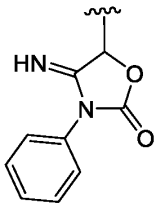
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

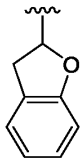
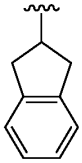
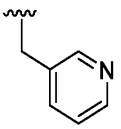
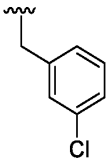
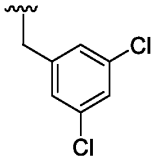
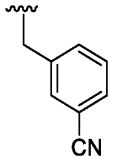
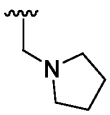
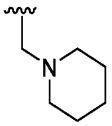
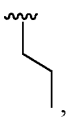
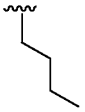
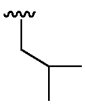
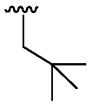
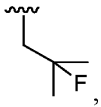
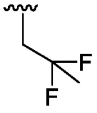
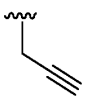
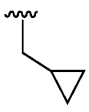
R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

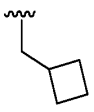
R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

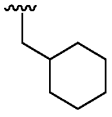
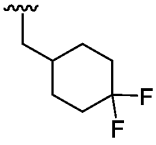
R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

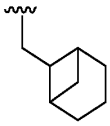
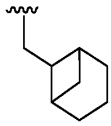
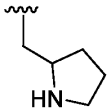
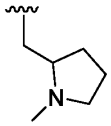
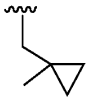
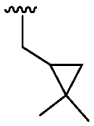
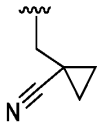
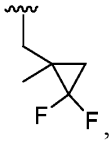
12. A is selected from the group consisting of -CN,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .













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13. R^{1a} is selected from the group consisting of

















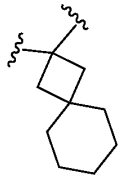




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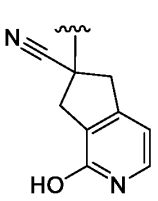
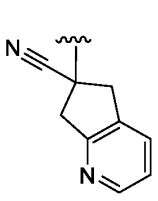
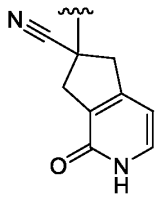
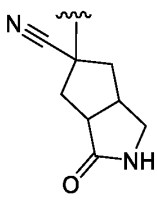
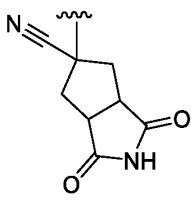
14. R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

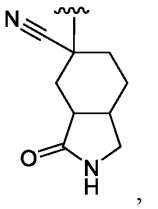
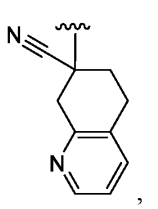
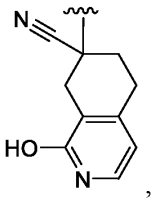
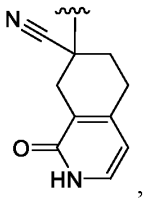
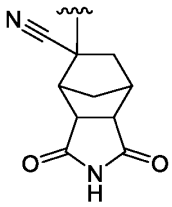
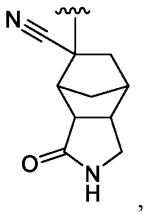
15. R^{1b} is hydrogen.

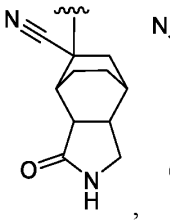
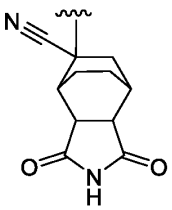
16. R^{1a} and R^{1b} are joined to together to form  .

17. R^{3a} is a 4-10 membered heterocycle substituted by A.

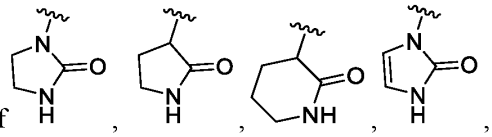
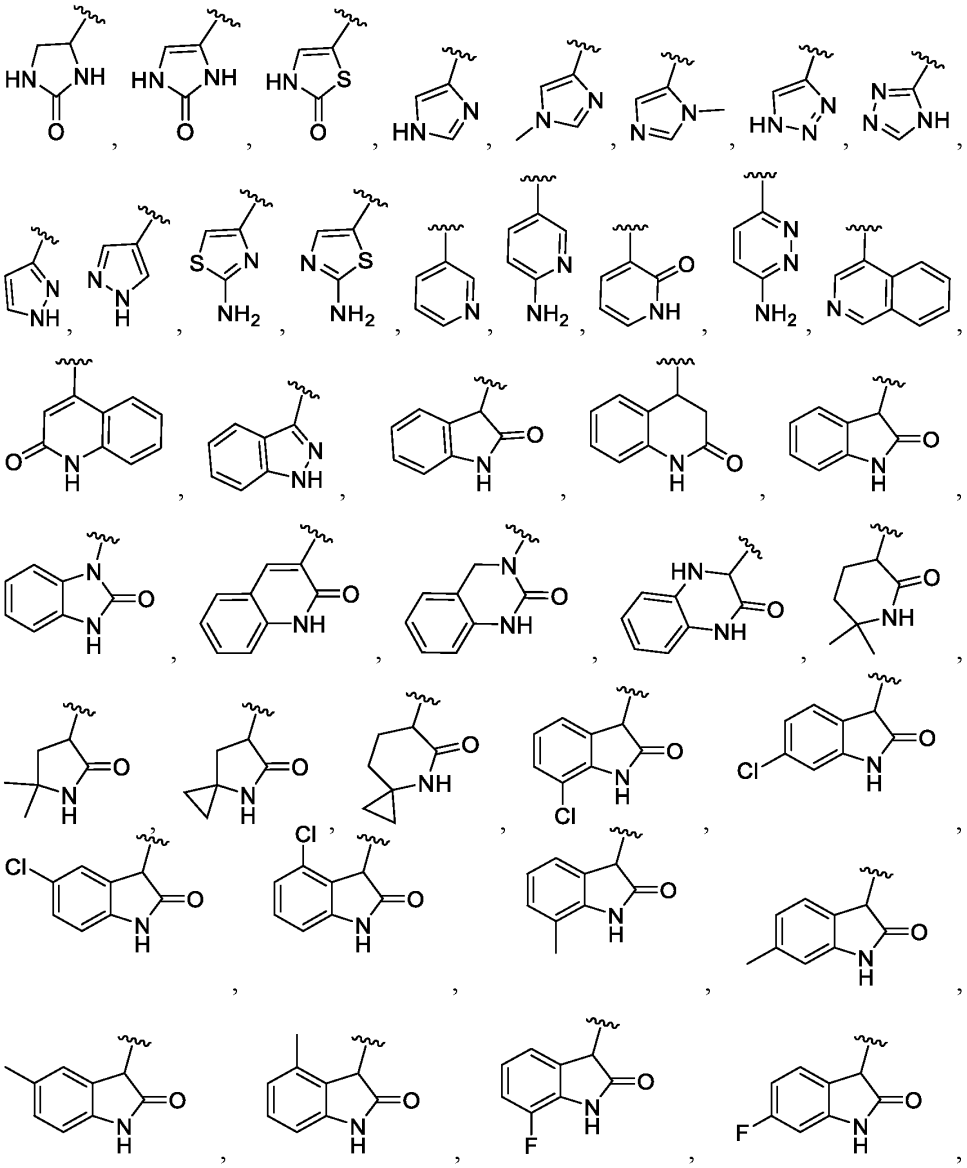
18. R^{3a} is selected from the group consisting of

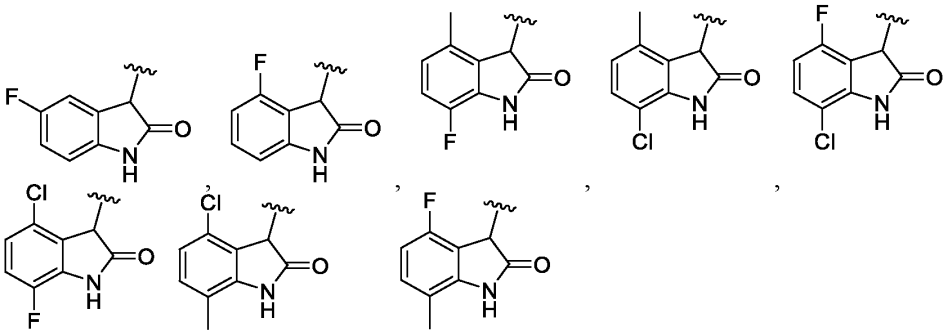
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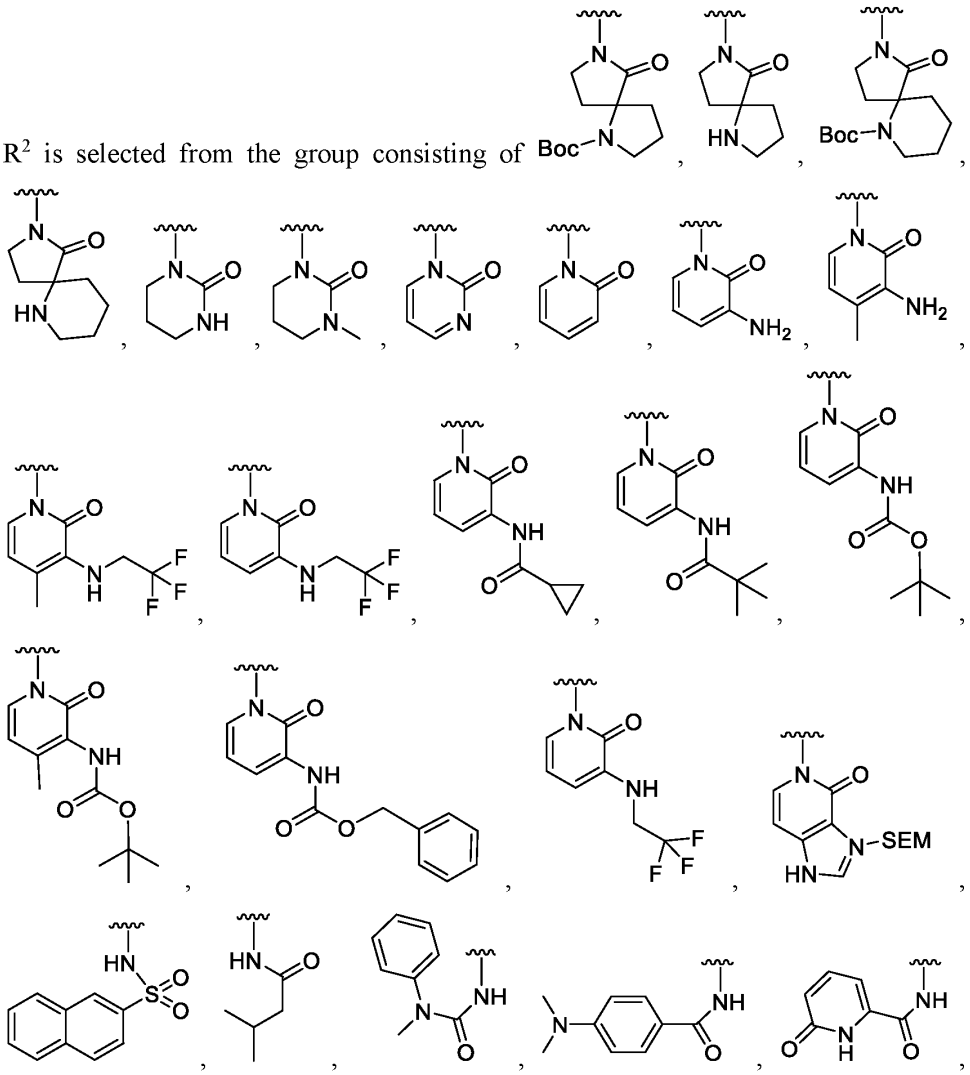
19. R^3 is a 4-10 membered heterocycle.

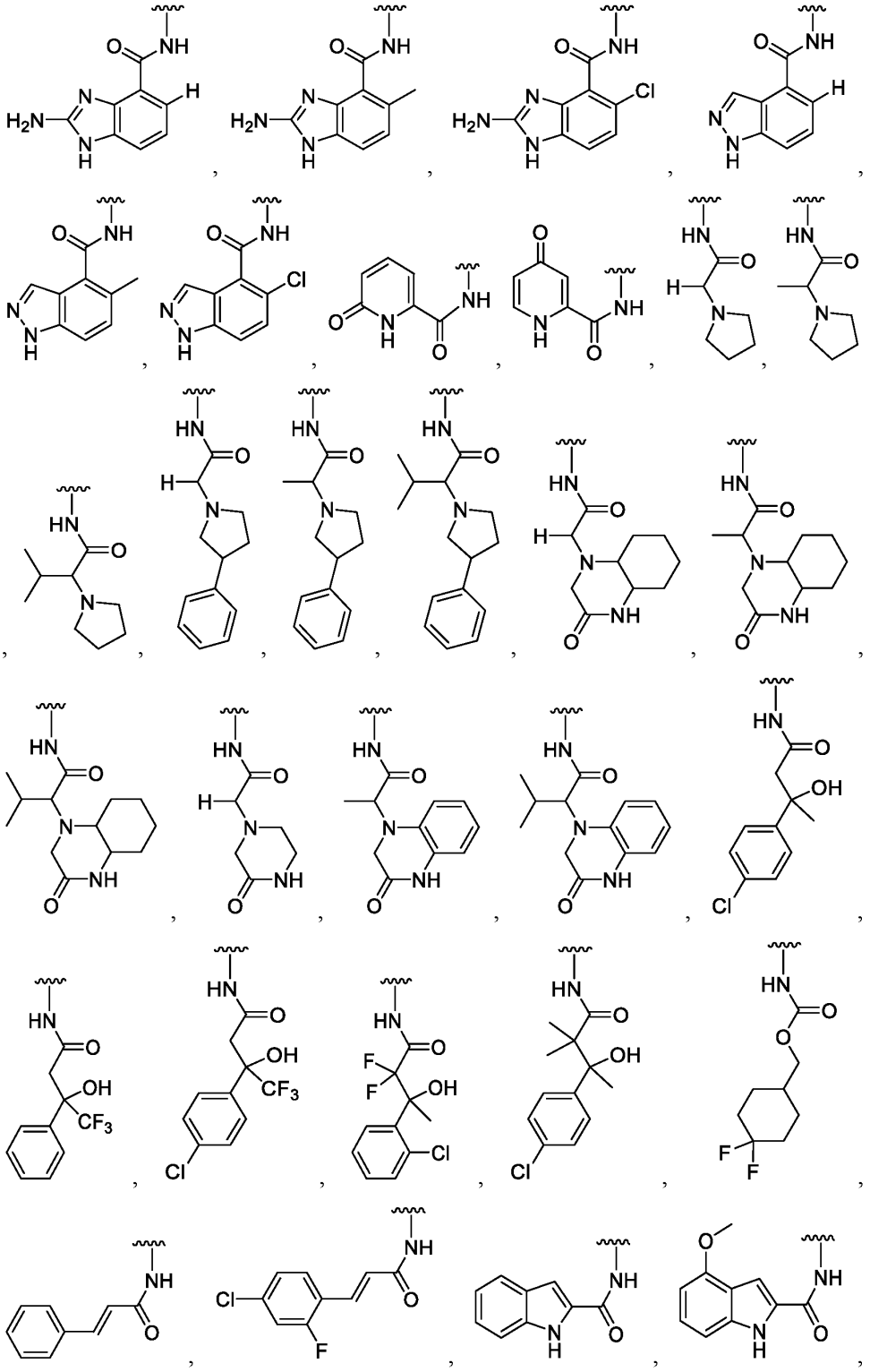
20. R^3 is selected from the group consisting of  , 

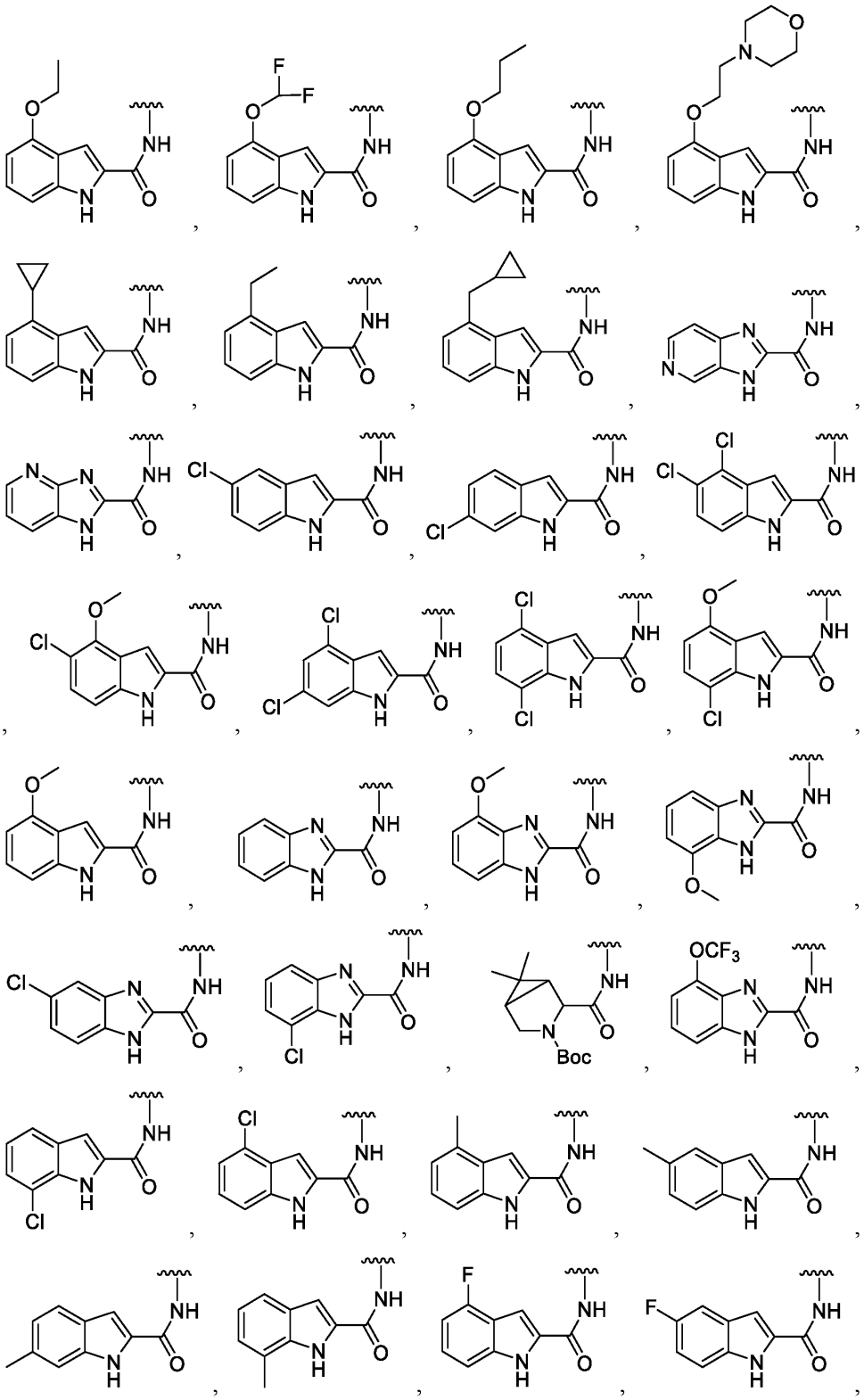


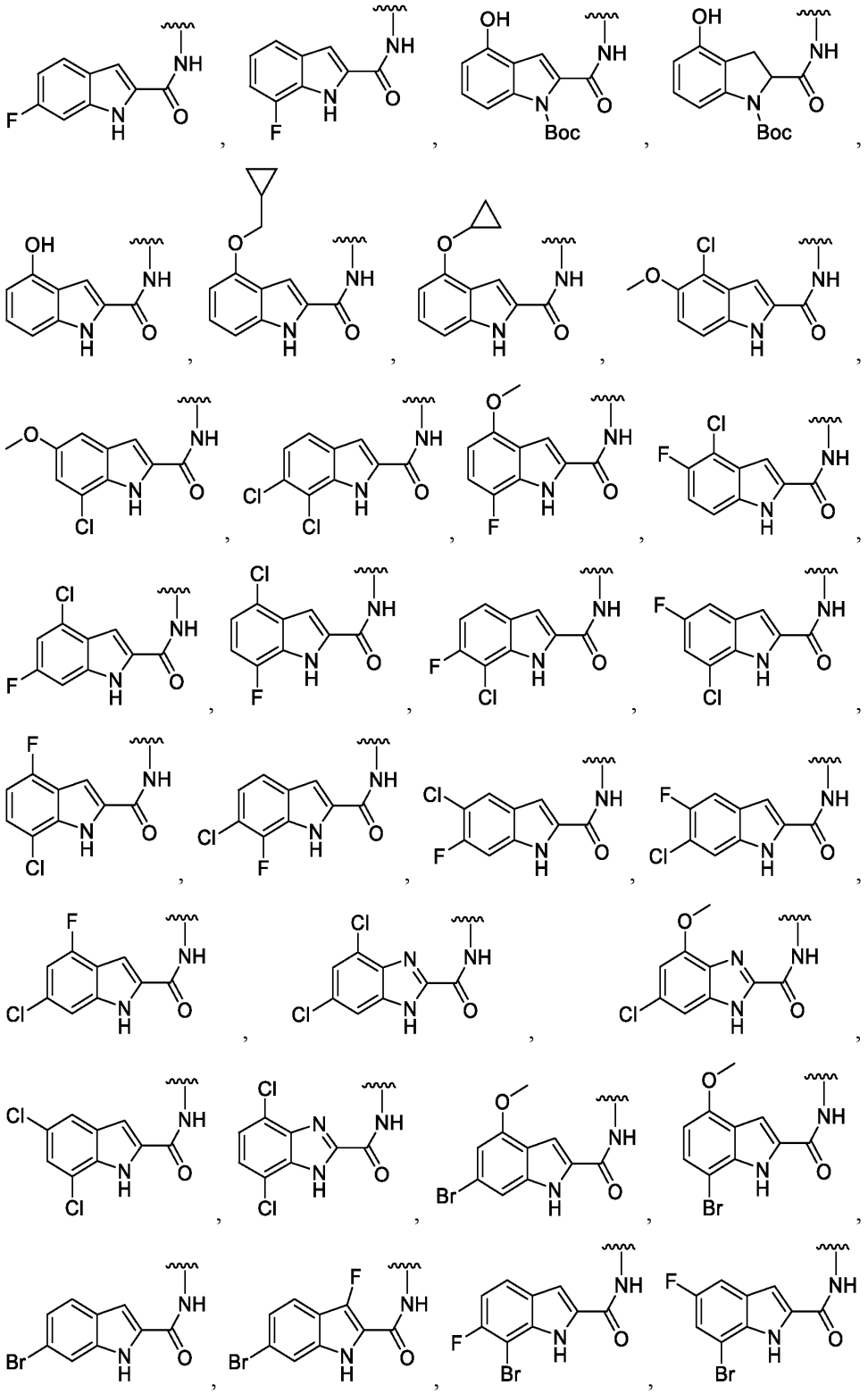
, and

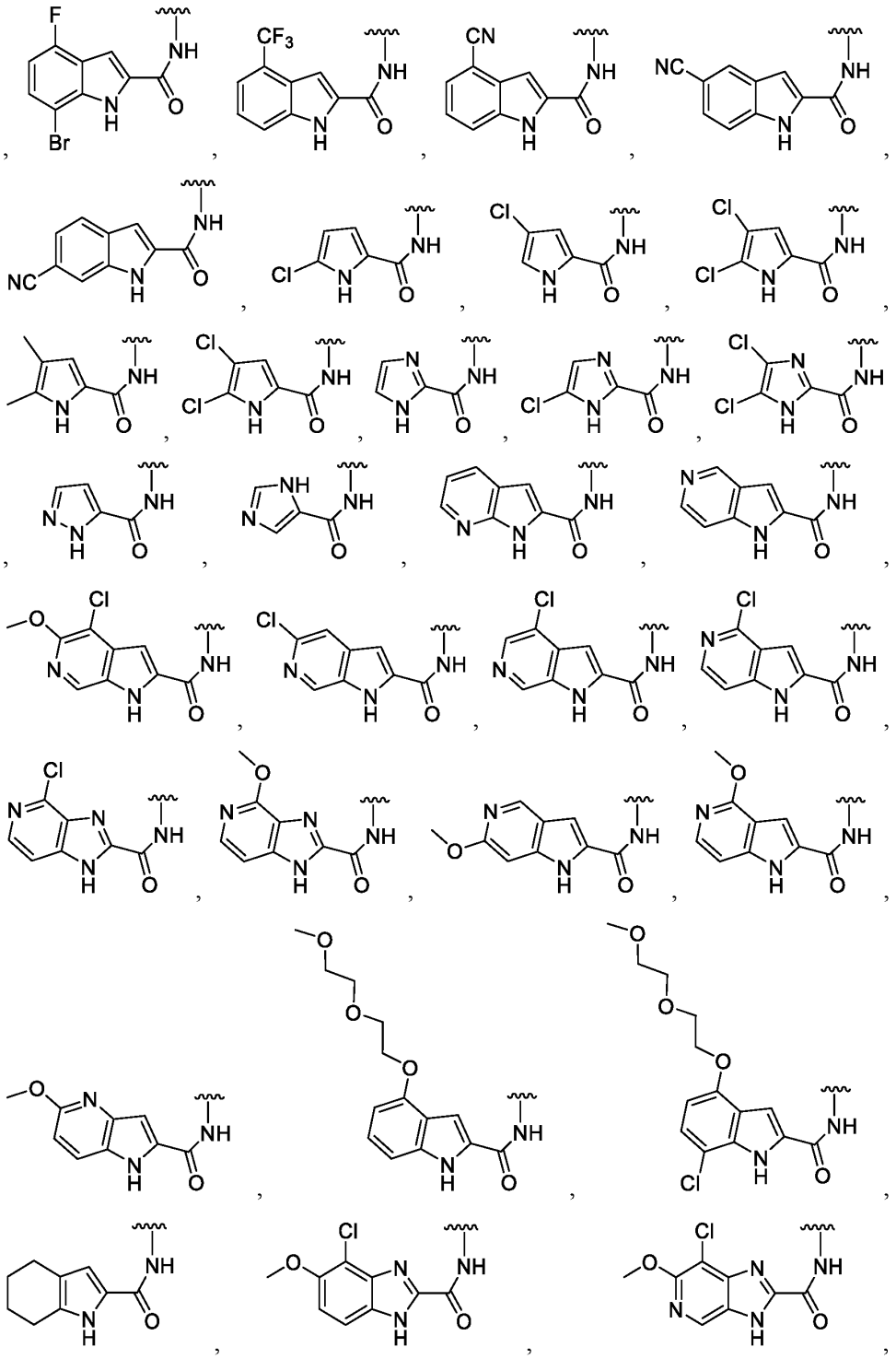
21. R^2 is selected from the group consisting of

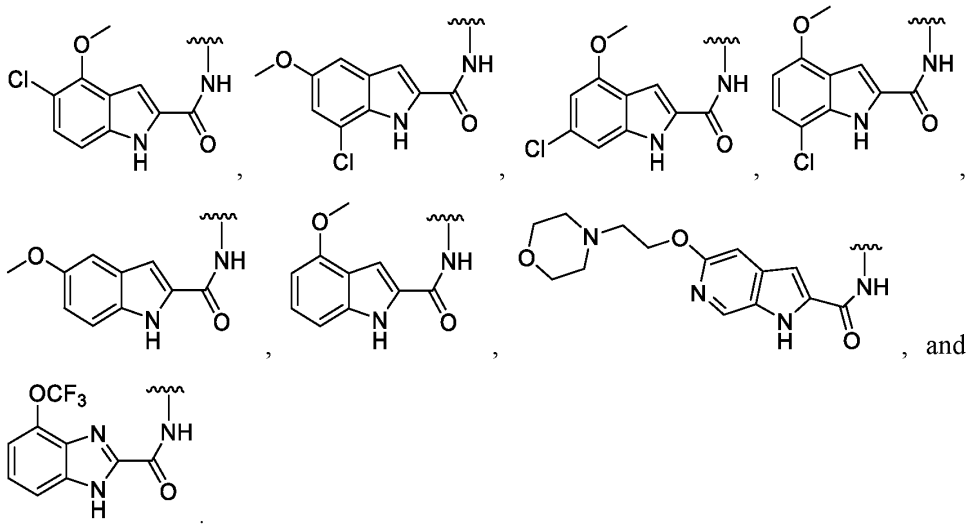




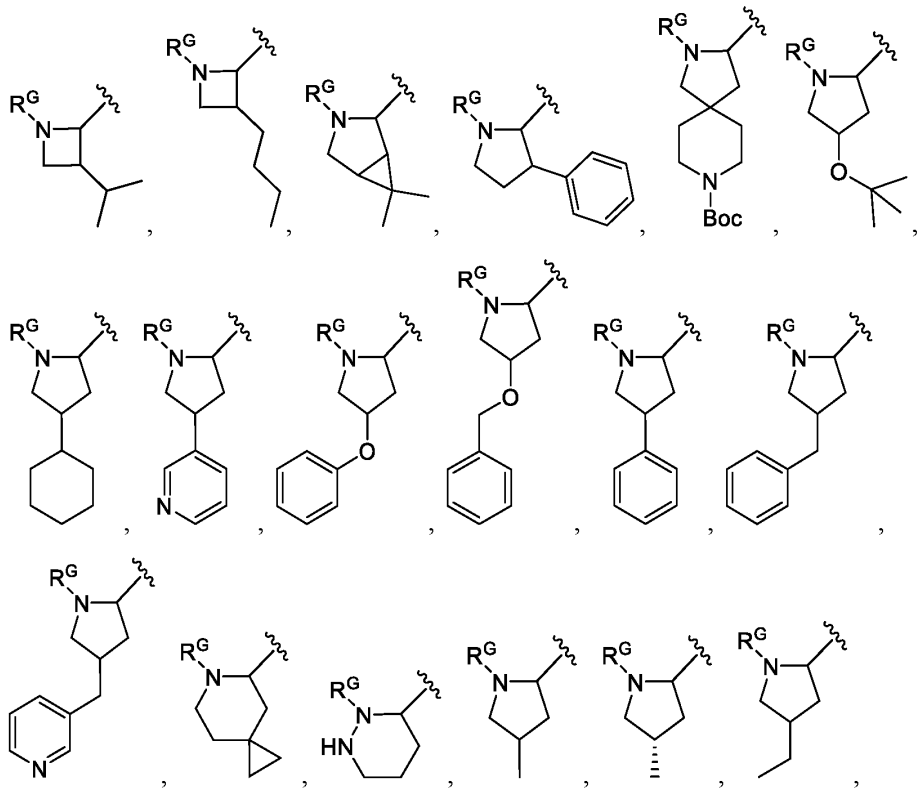


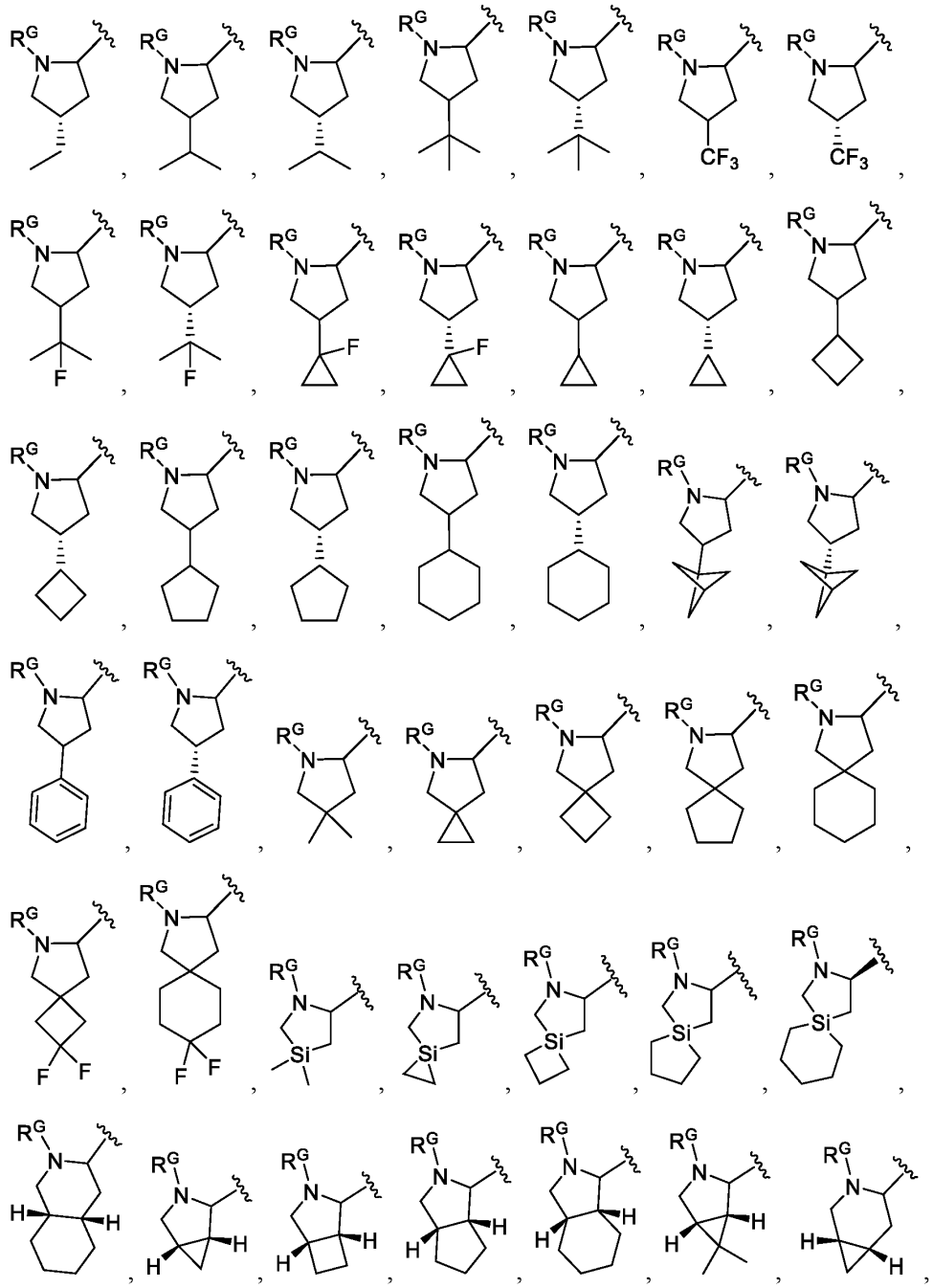


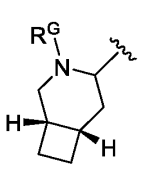
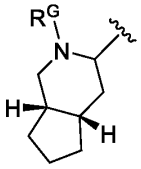
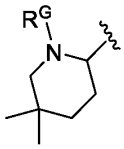
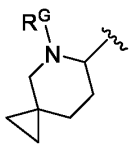
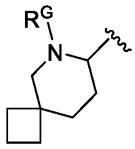
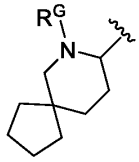
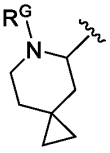




22. R^{1a} and R^2 are joined to together to form the heterocycle selected from the group consisting of:

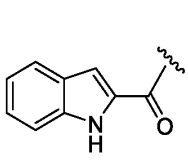
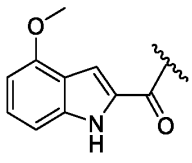
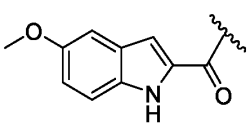
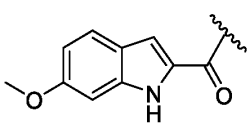
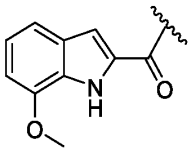
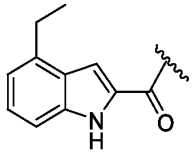


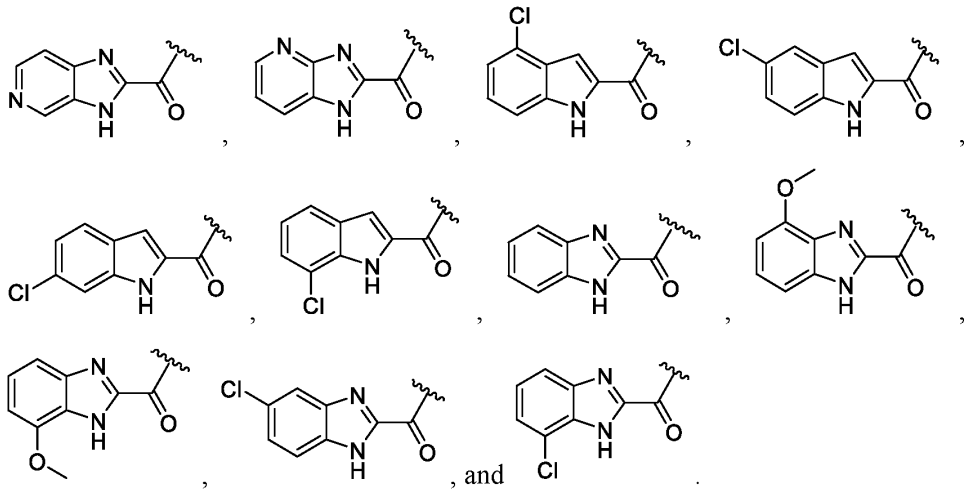



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; and R^{1b} is H.

23. R^G is selected from the group consisting of H, C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of -C(=O), halo, cyano, $-NR^mR^m$, and -NH(C=O)R^m) and C(=O)-C_{1-6}alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, cyano, $-NR^mR^m$, $-NR^m(C=O)R^m$, phenyl, cycloalkyl and heterocycle, wherein R^m is selected for each occurrence by H or C_{1-3}alkyl (optionally substituted by one, two or three halogens, e.g., F), or C_3-C_6cycloalkyl (optionally substituted by one, two, or three F).

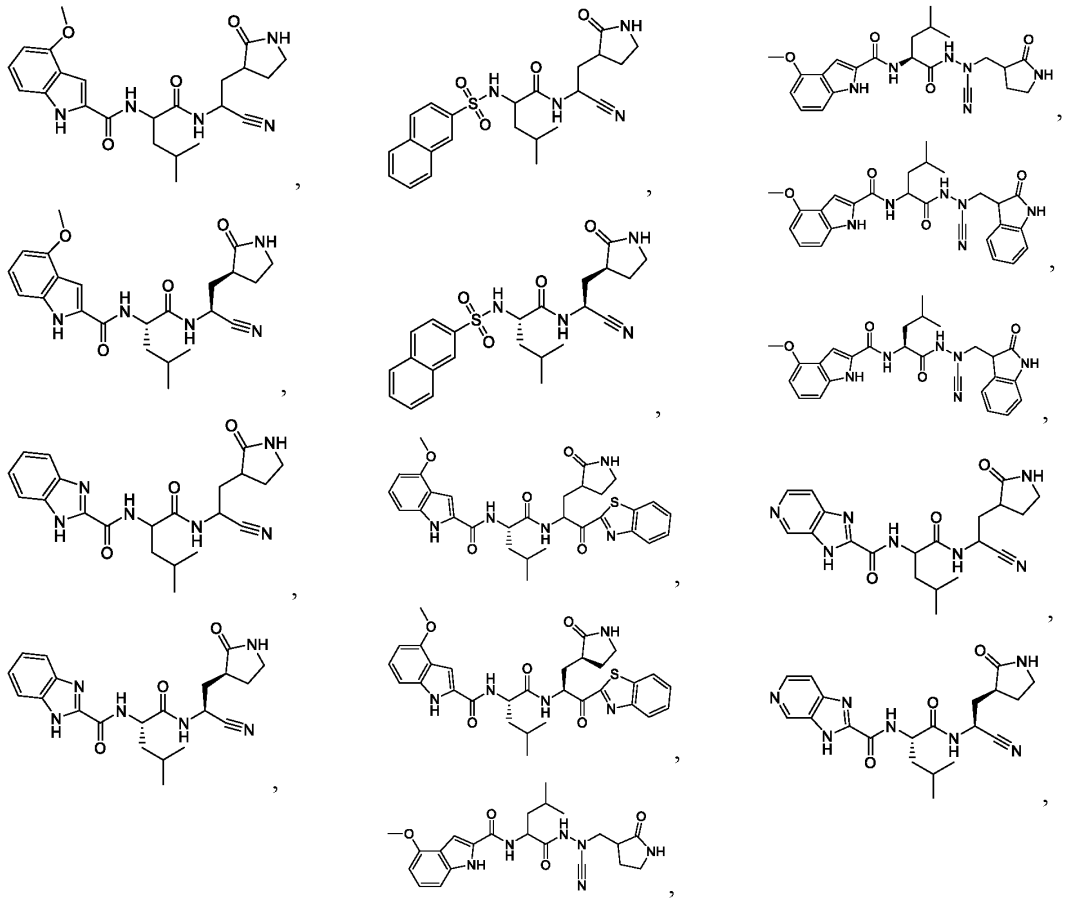
24. R^G is selected from the group consisting of a -C(O)-monocyclic 5-6 membered or -C(O)-bicyclic heteroaryl each having at least one ring nitrogen and optionally substituted by one two or three substitutents each selected from halo, methoxy, cyano, and hydroxyl; and $-C(O)-C(R^{55}R^{56})-NH-C(O)-R^{57}$, wherein R^{55} is H and R^{56} is a straight or branched C_1-C_5alkyl (optionally substituted by halo), or R^{55} and R^{56} taken together with the carbon to which they are attached form a C_3-C_5cycloalkyl (optionally substituted by halo) and wherein R^{57} is C_1-C_3alkyl (optionally substituted by one, two or three halo).

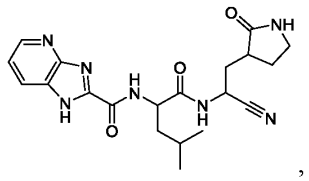
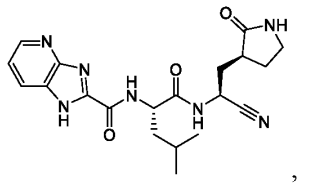
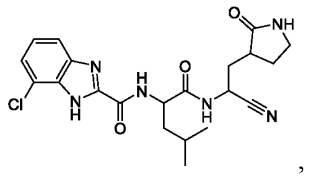
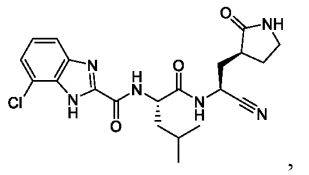
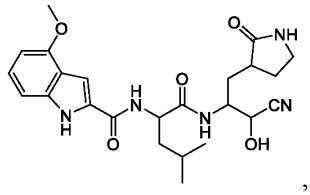
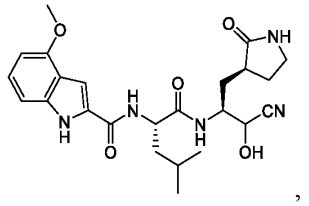
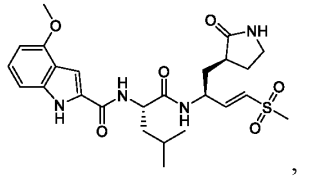
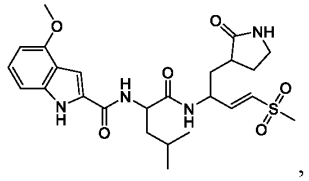
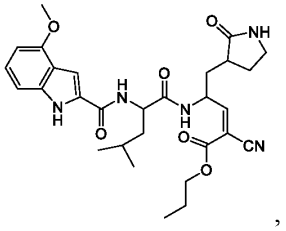
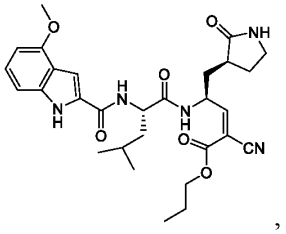
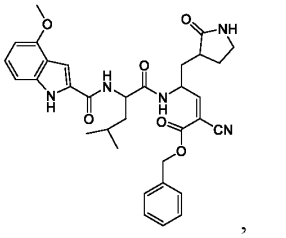
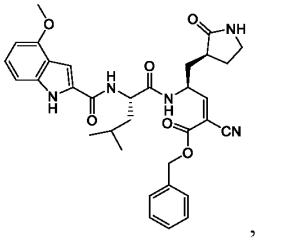
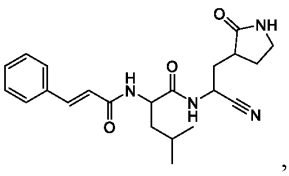
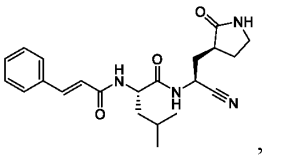
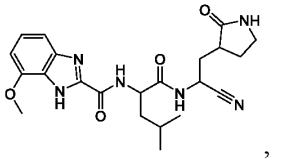
25. R^G is selected from the group consisting of

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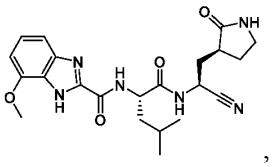
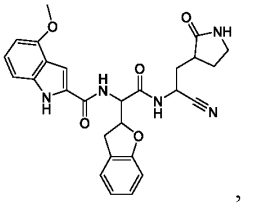
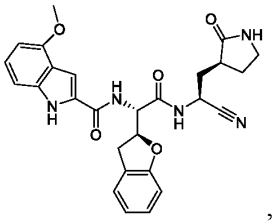
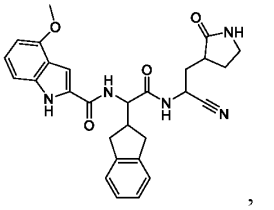
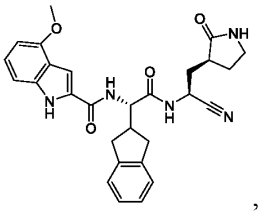
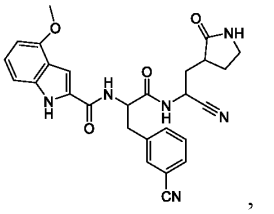
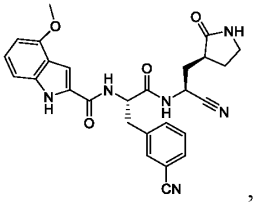


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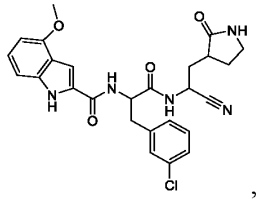
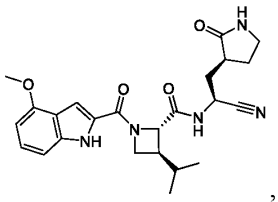
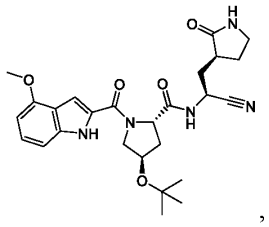
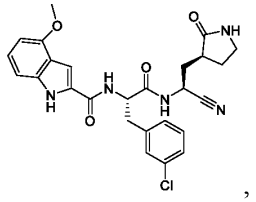
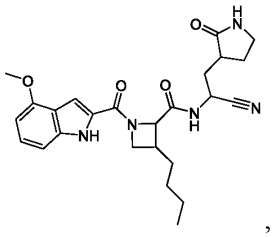
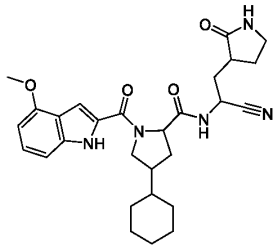
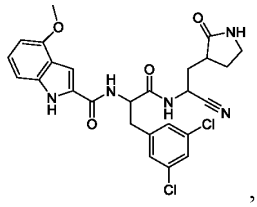
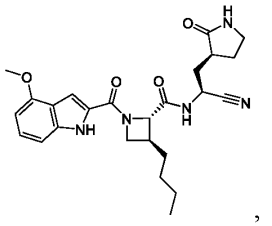
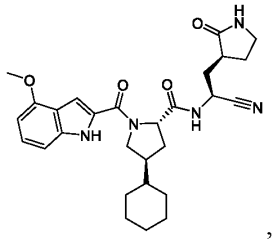
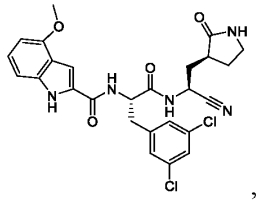
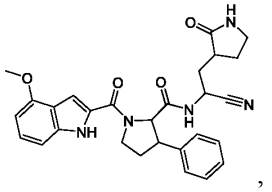
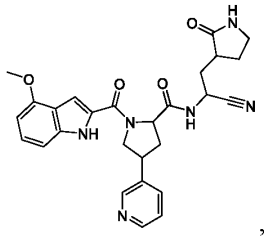
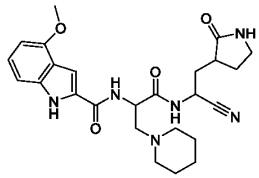
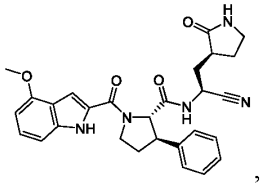
26. A compound selected from the group consisting of:




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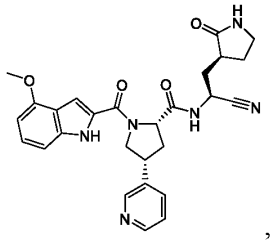
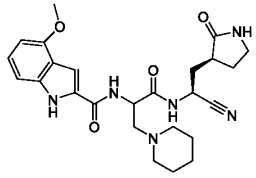
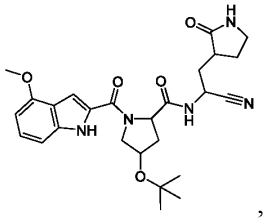
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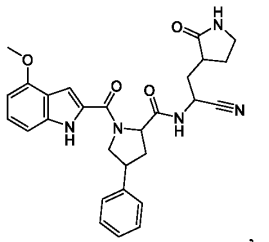
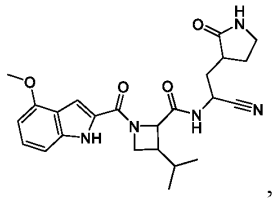
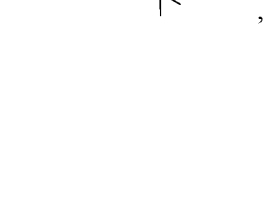
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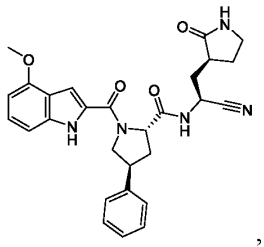
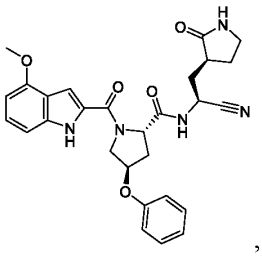
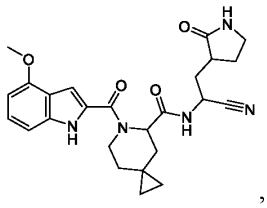
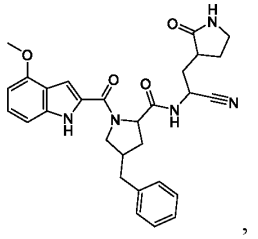
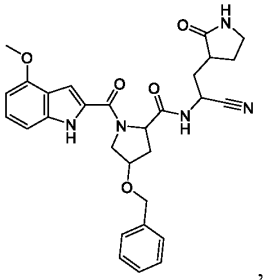
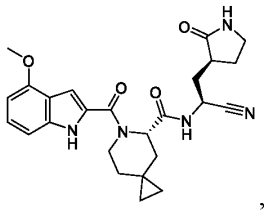
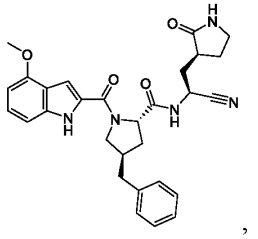
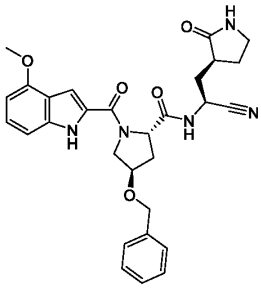
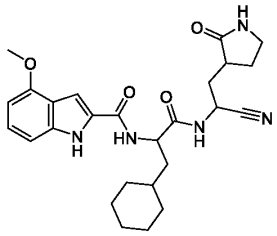
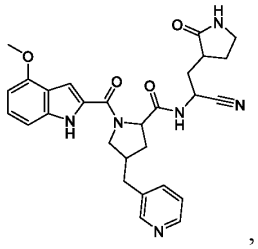
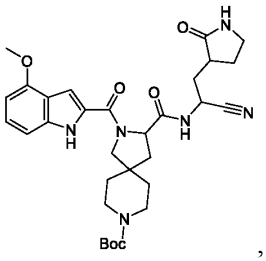
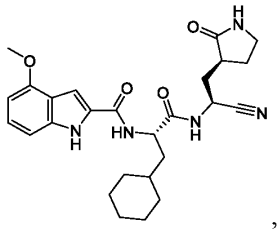
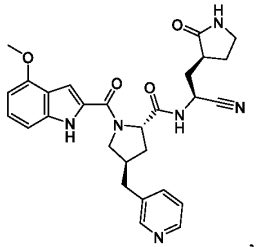
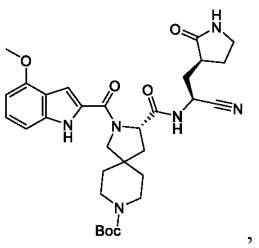
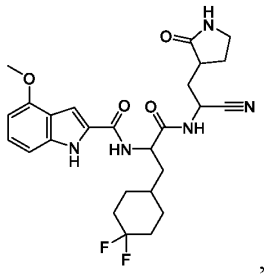
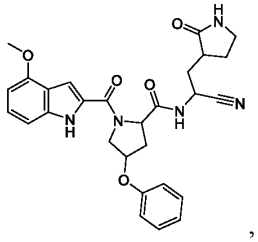
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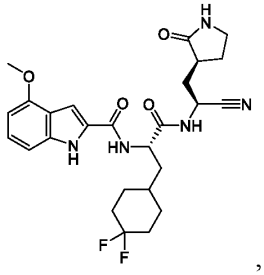
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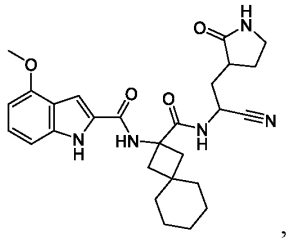
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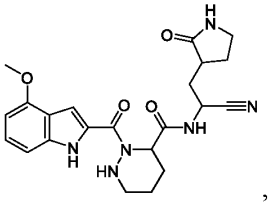
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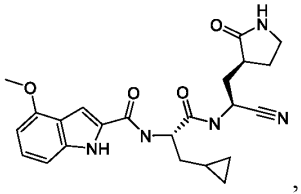
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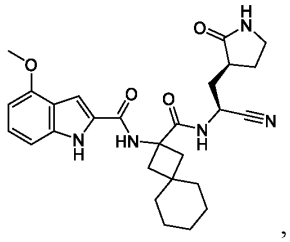
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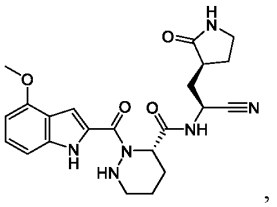
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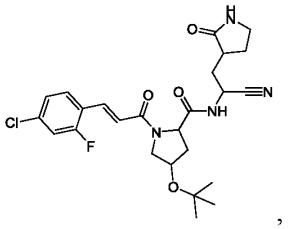
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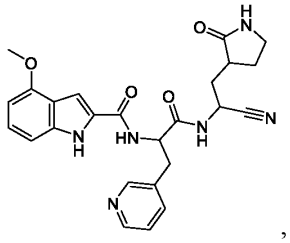
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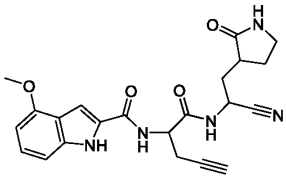
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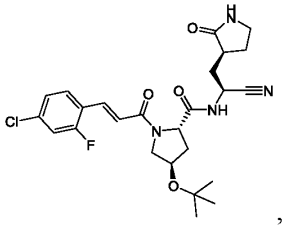
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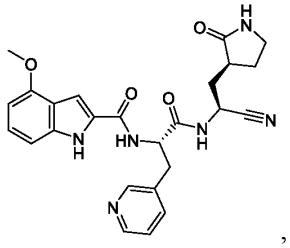
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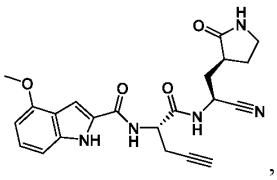
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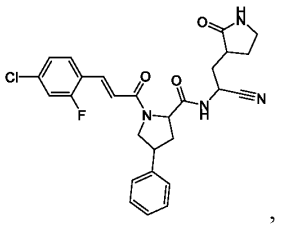
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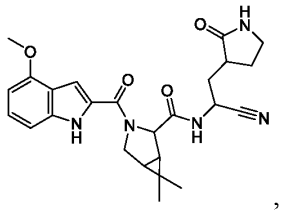
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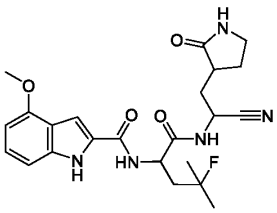
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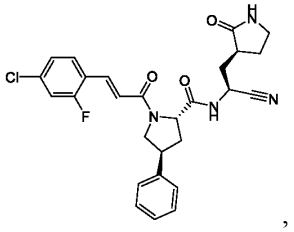
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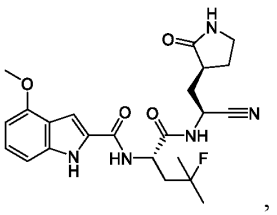


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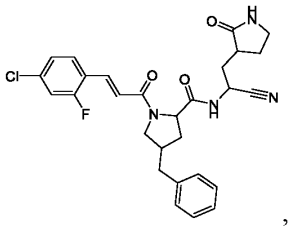


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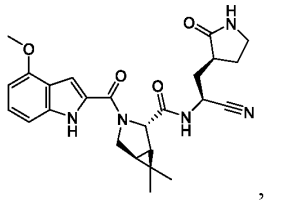
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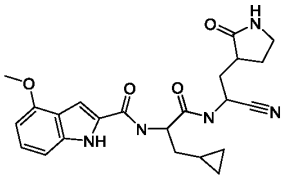


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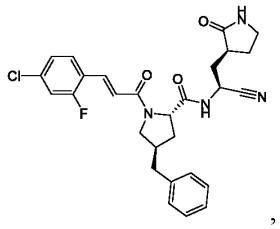
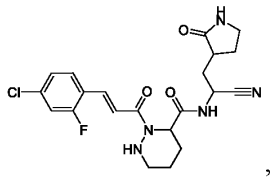
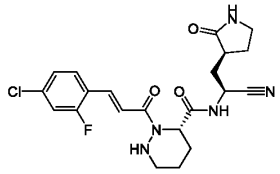
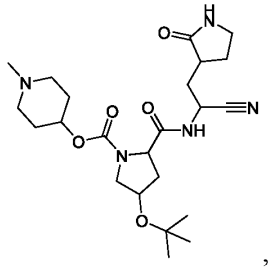
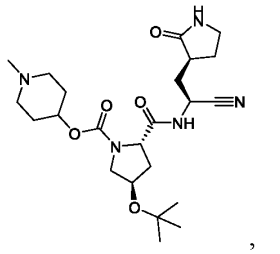
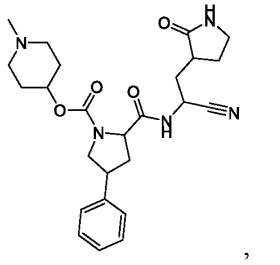
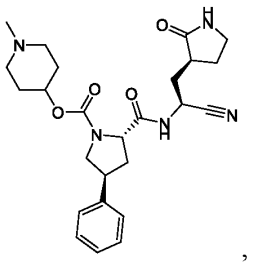
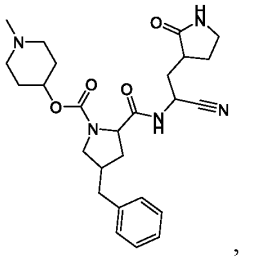
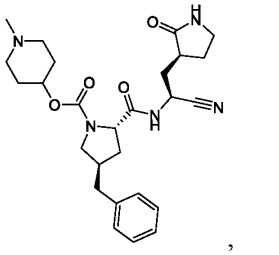
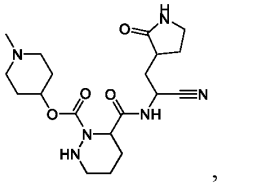
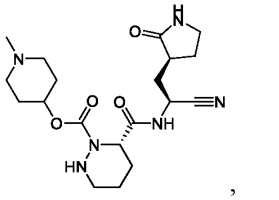
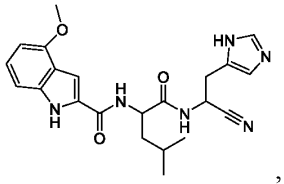
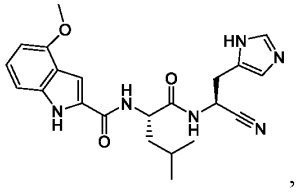
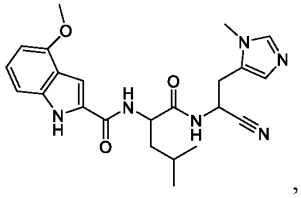
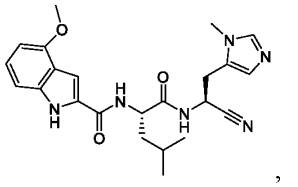
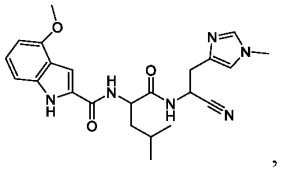
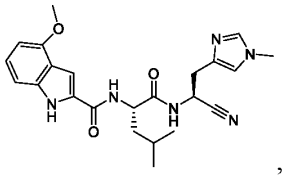
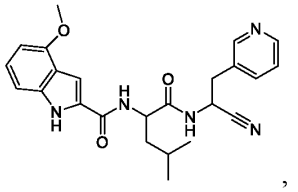
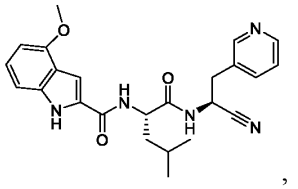
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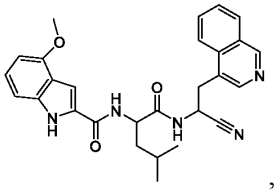
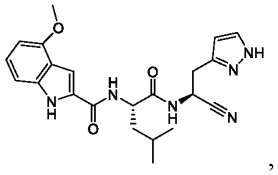
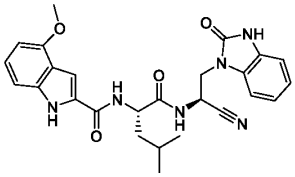
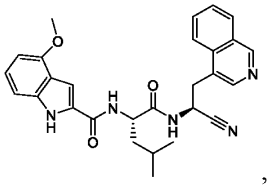
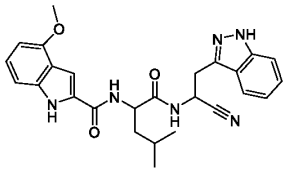
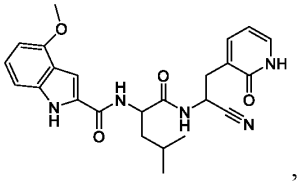
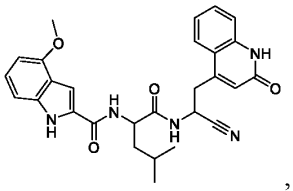
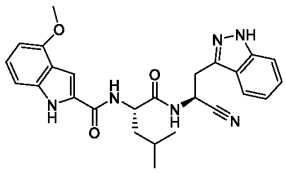
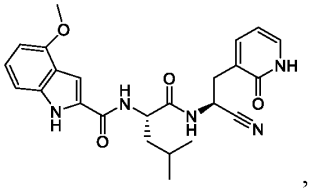
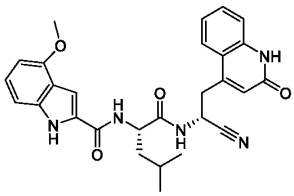
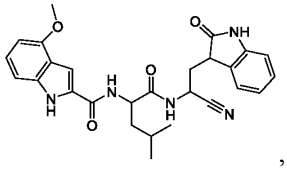
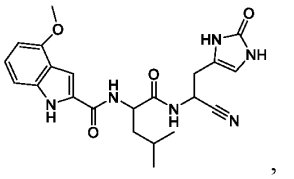
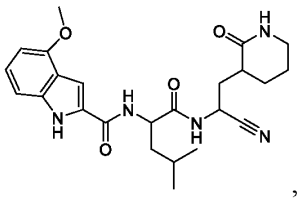
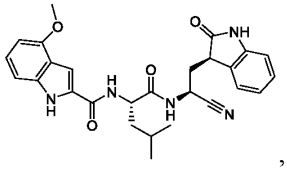
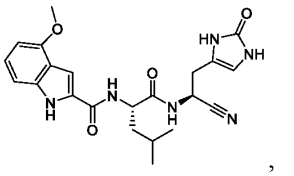
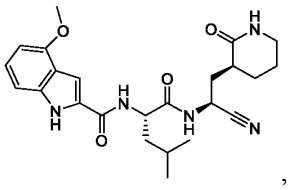
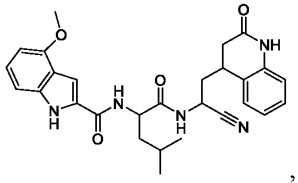
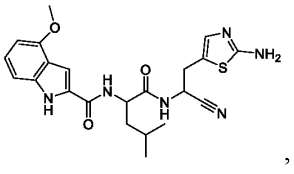
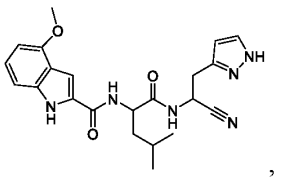
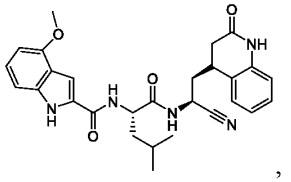
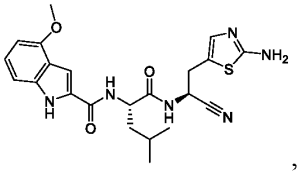
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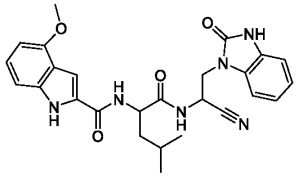
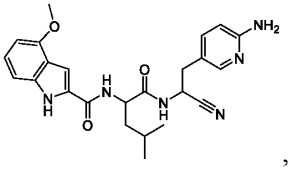


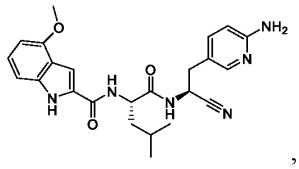
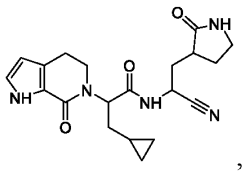
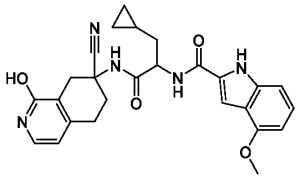
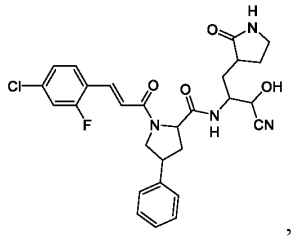
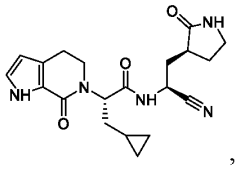
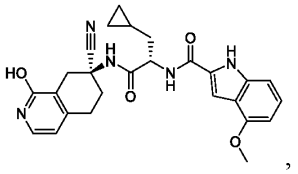
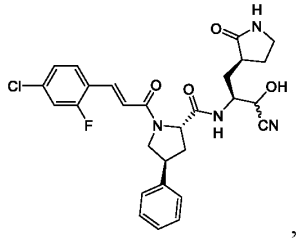
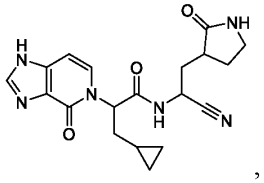
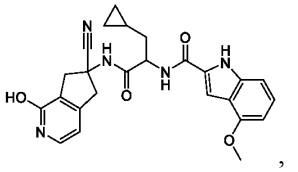
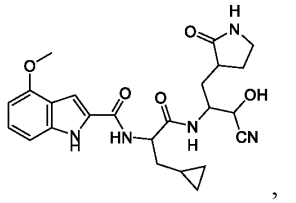
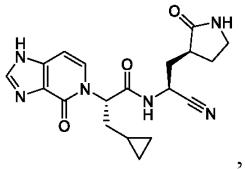
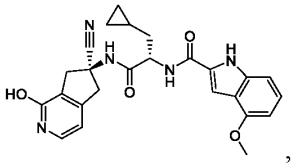
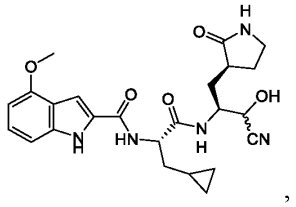
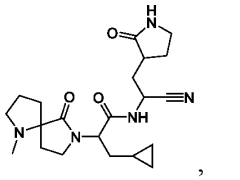
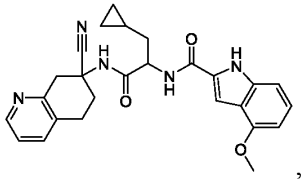
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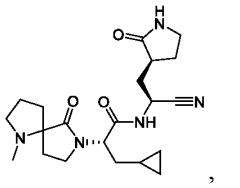
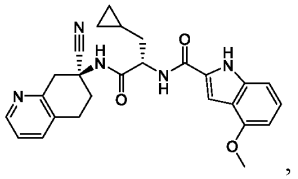
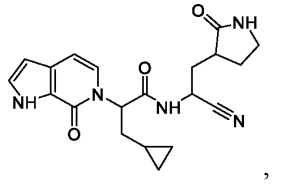
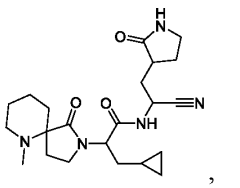
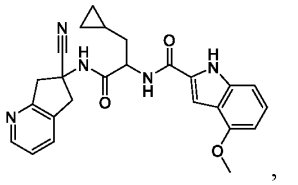
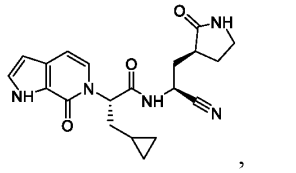
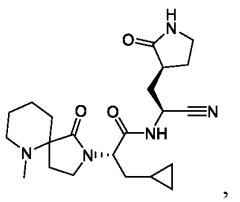
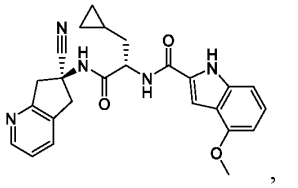
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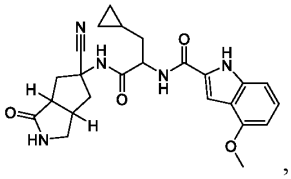
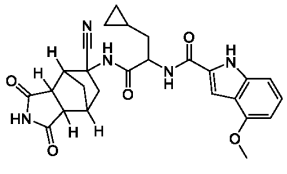
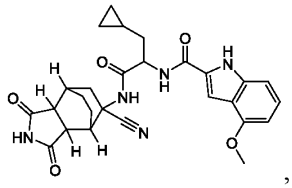
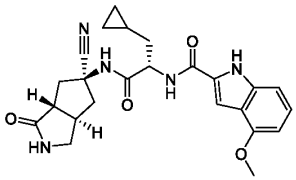
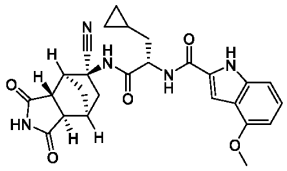
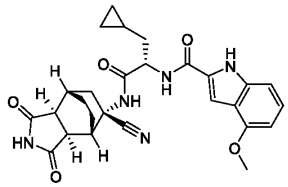
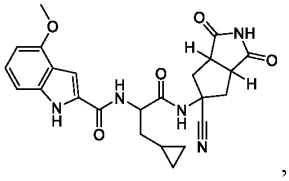
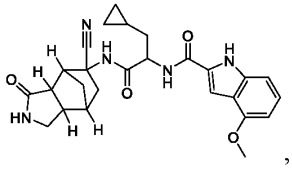
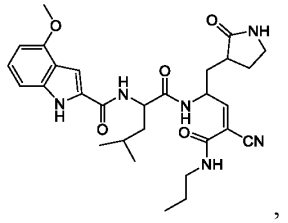
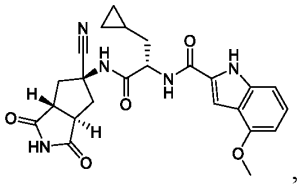
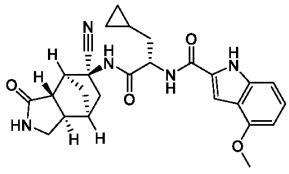
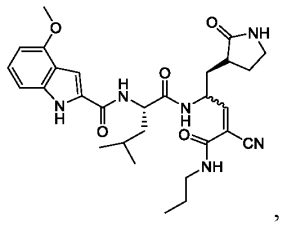
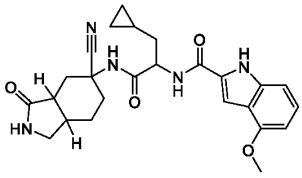
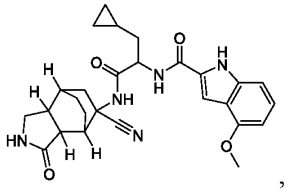
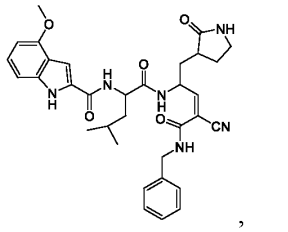
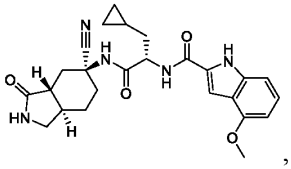
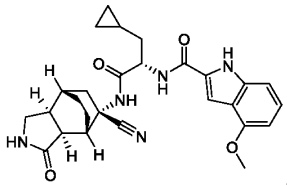
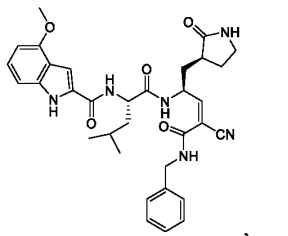
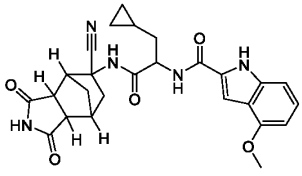
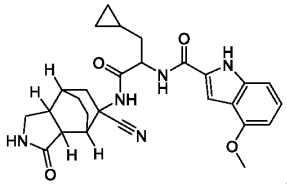

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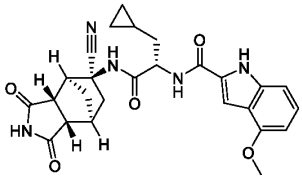
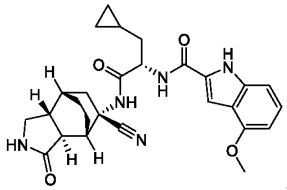
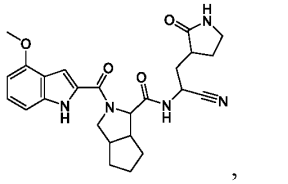

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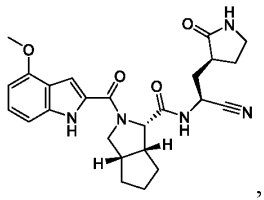
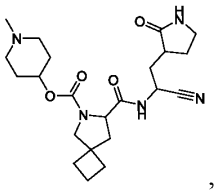
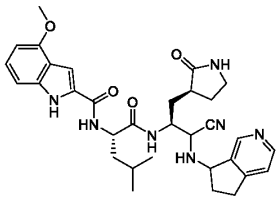
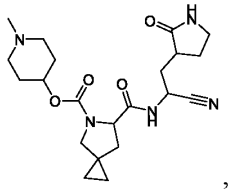
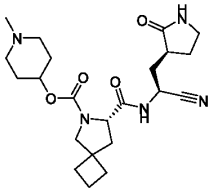
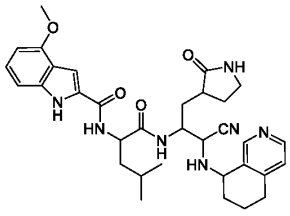
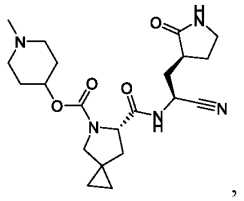
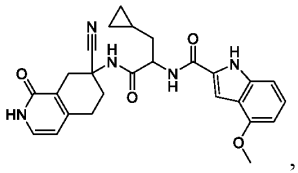
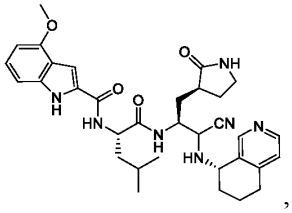
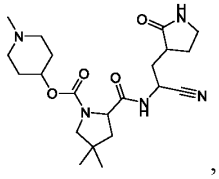
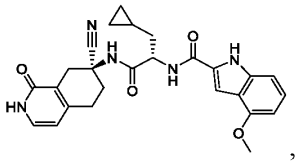
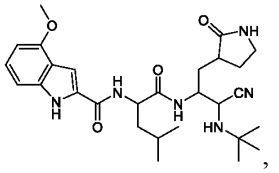
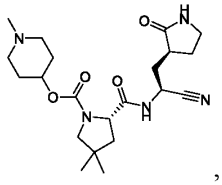
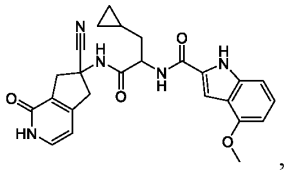
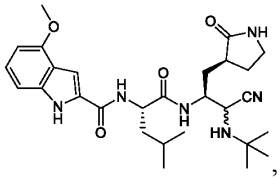
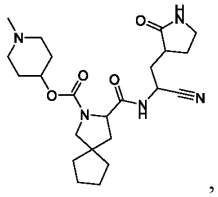
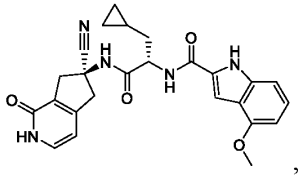
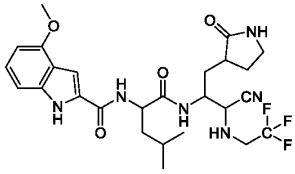
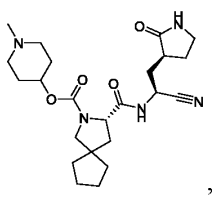
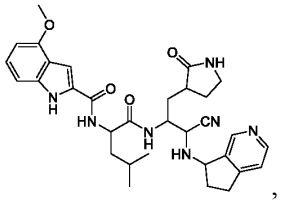
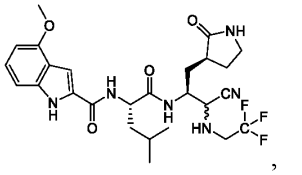
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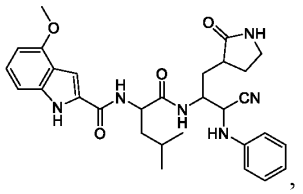
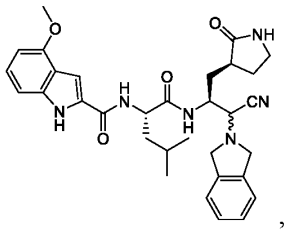
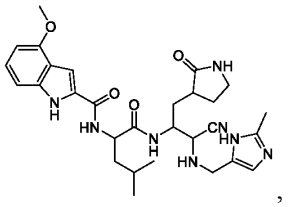
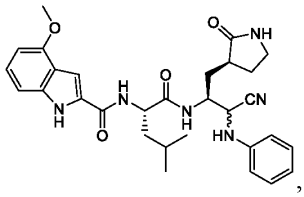
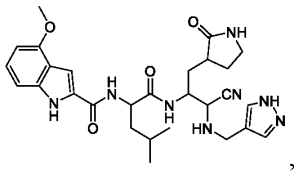
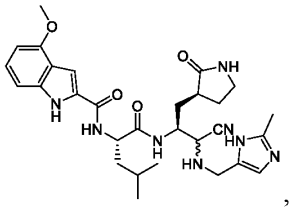
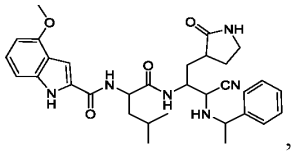
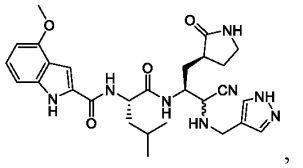
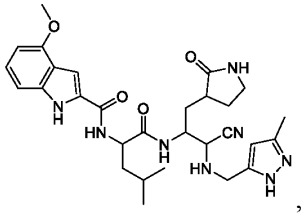
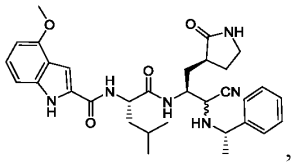
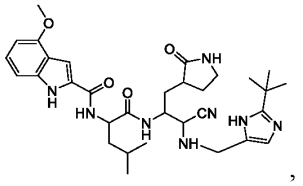
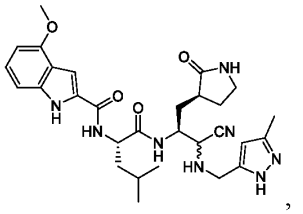
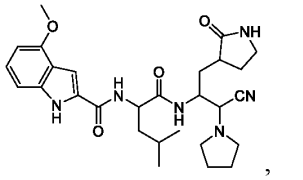
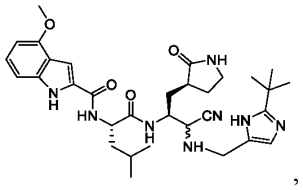

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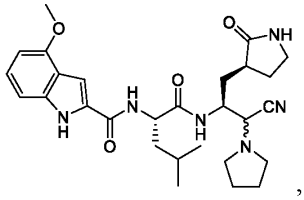
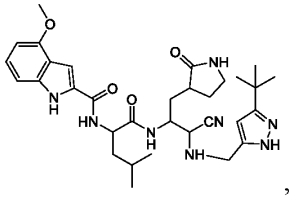
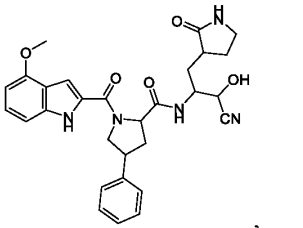
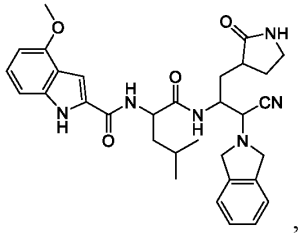
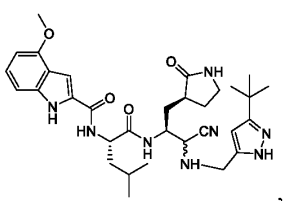
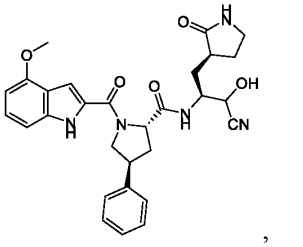
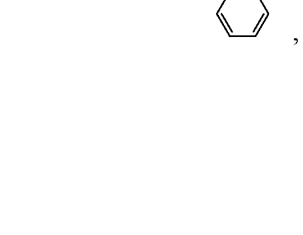
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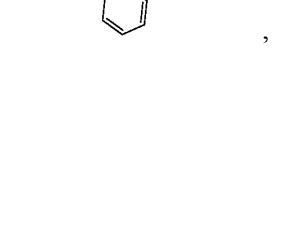

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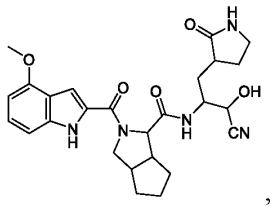
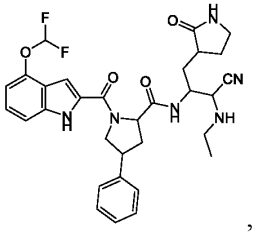
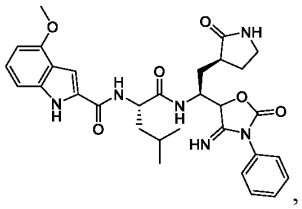
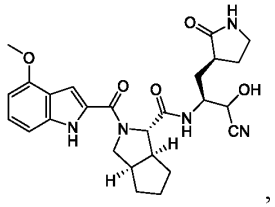
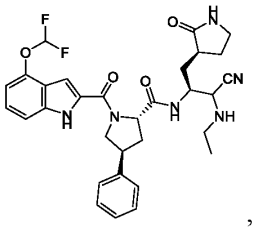
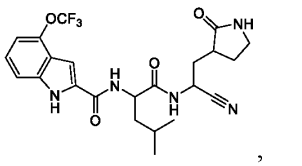
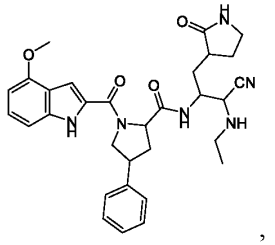
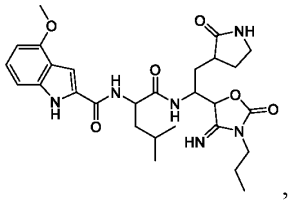
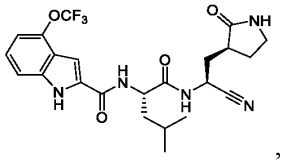
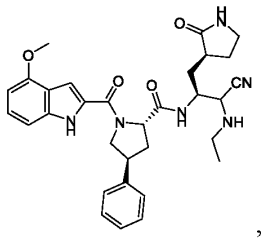
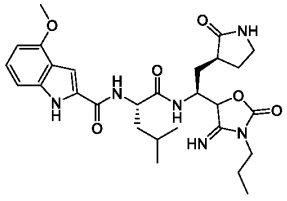
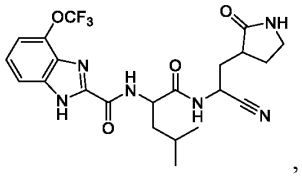
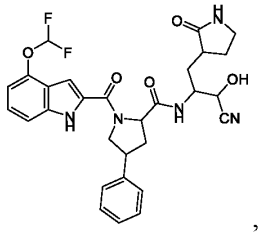
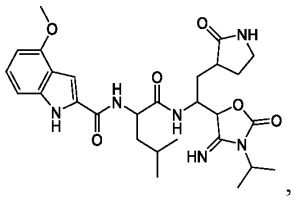
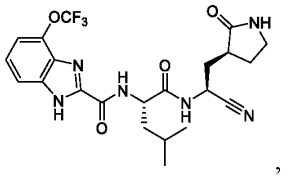
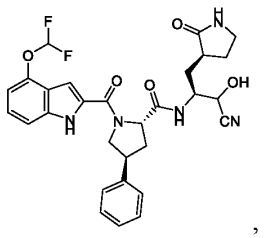
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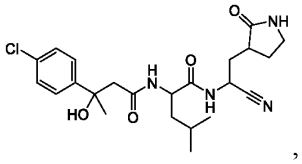
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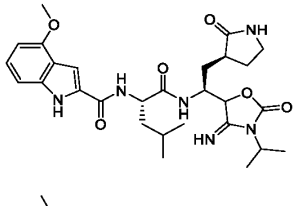
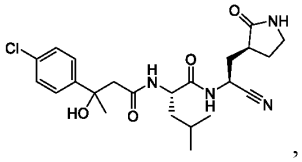
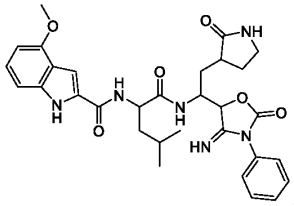
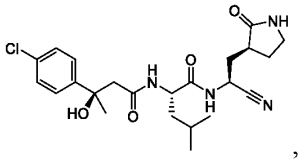

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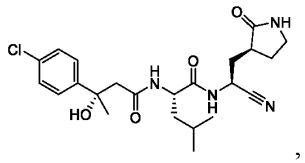
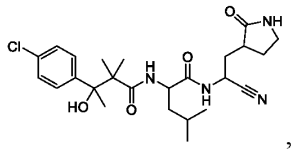
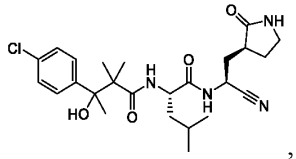
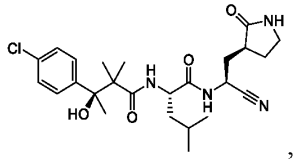
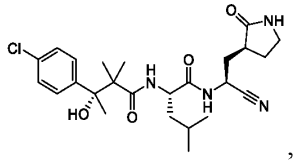
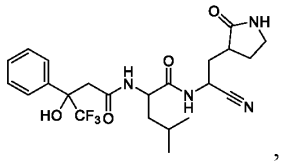
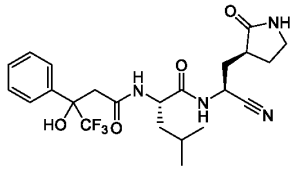
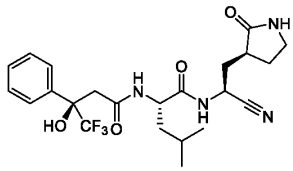
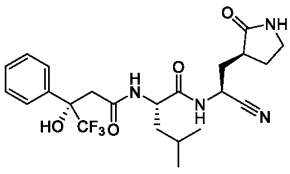
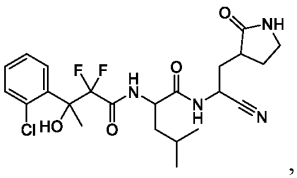
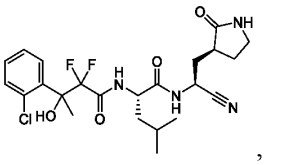
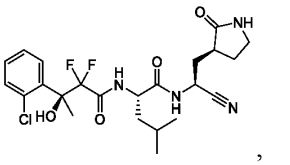
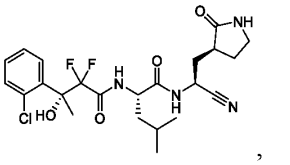
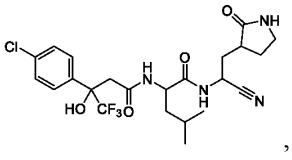
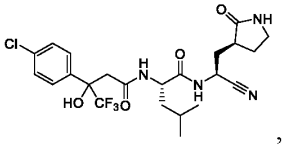
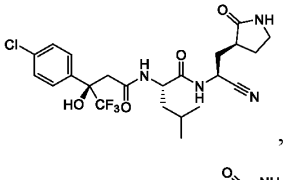
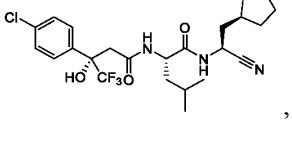
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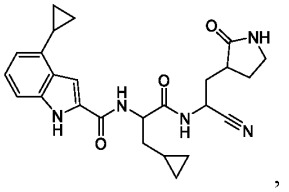
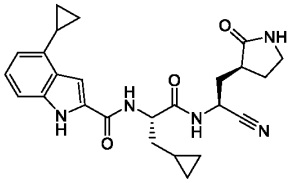
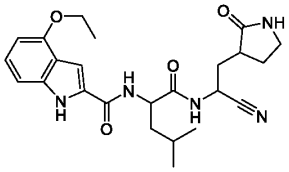
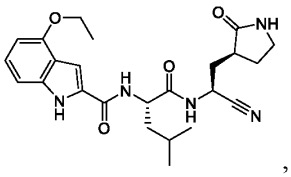
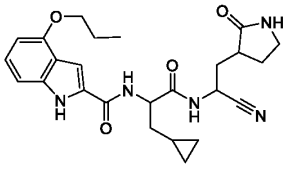
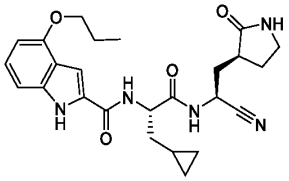
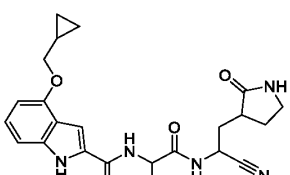
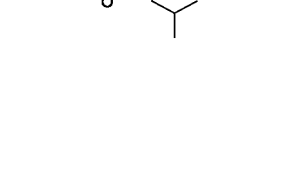
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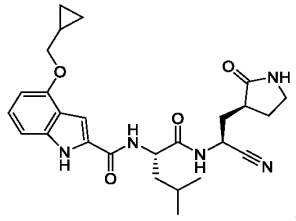

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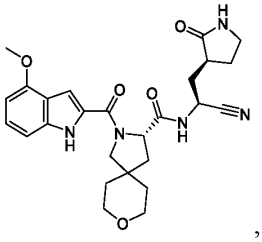
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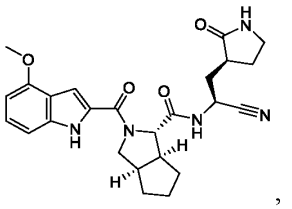
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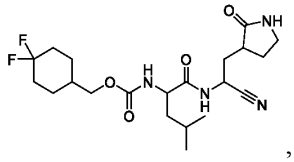
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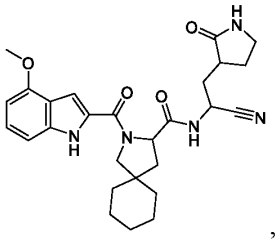
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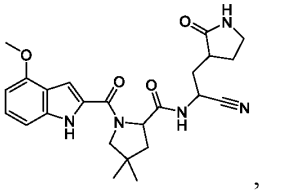
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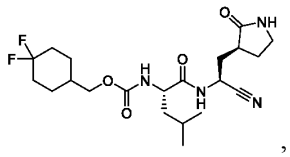
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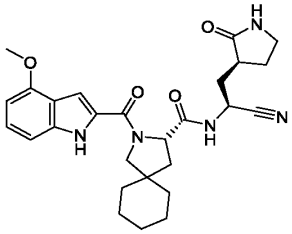
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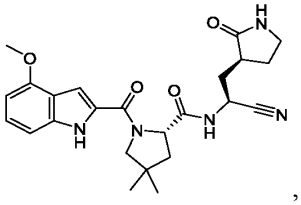
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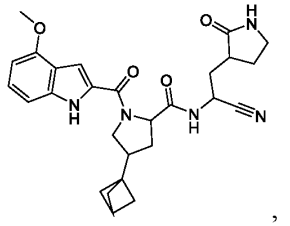
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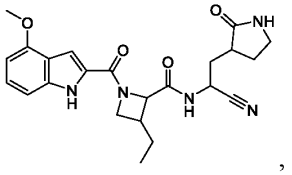
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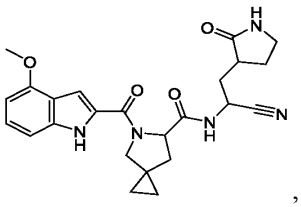
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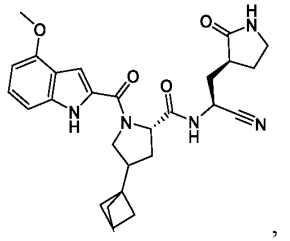
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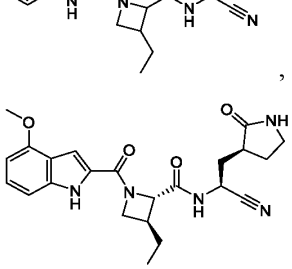
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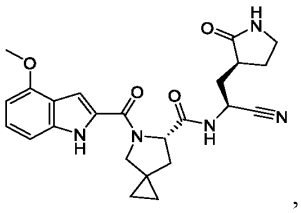
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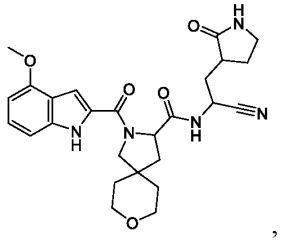
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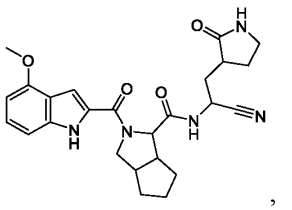
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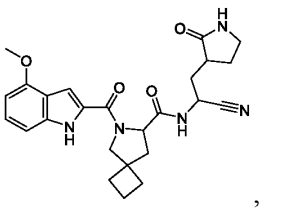
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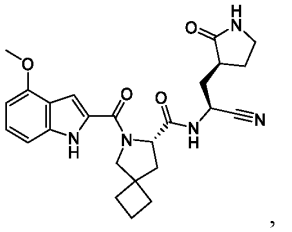
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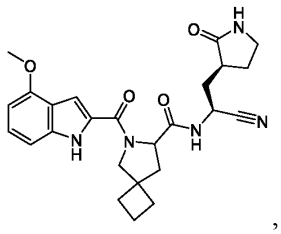
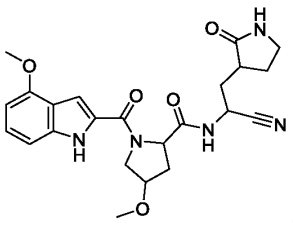
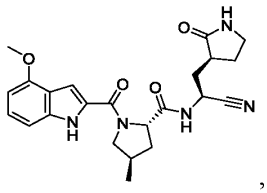
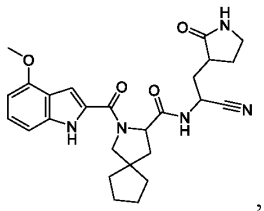
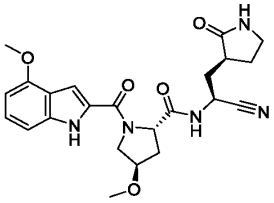
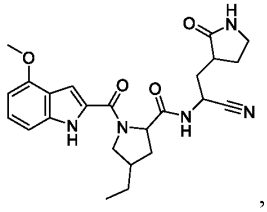
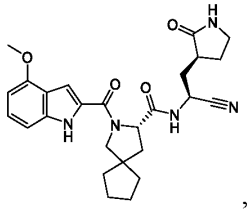
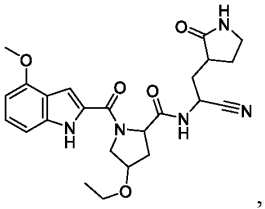
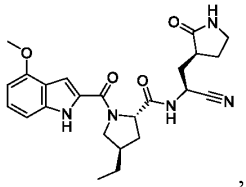
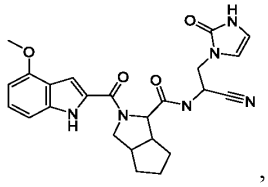
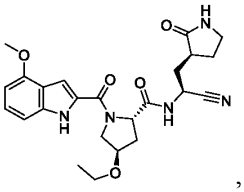
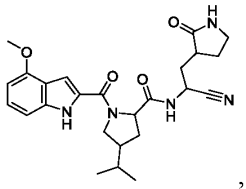
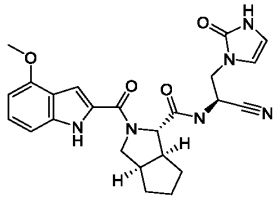
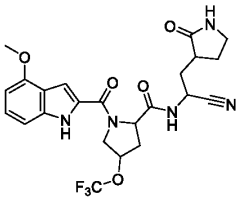
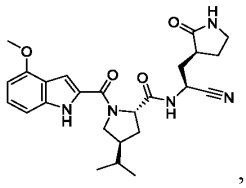
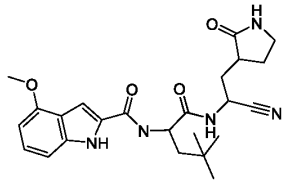
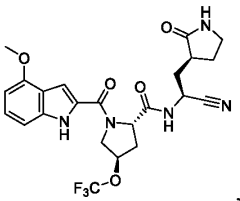
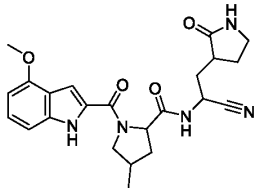
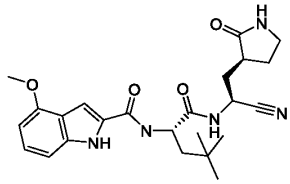
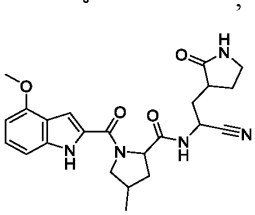
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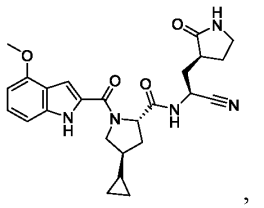


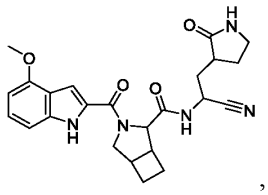
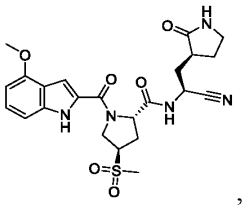
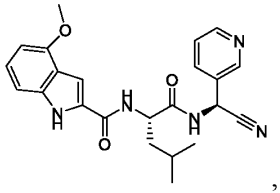
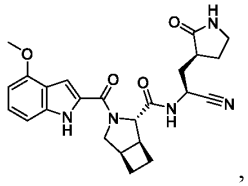
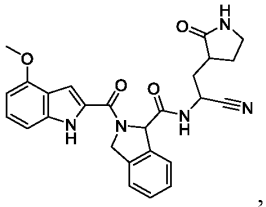
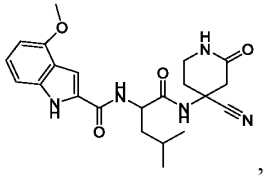
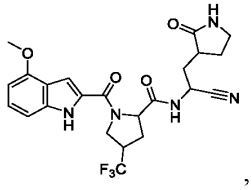
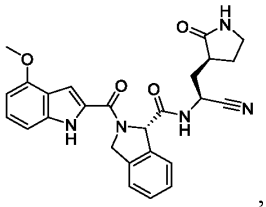
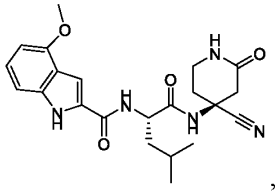
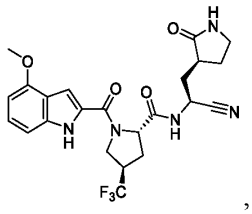
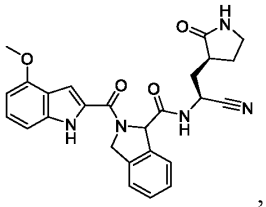
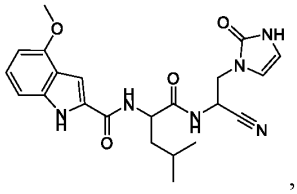
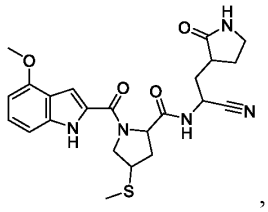
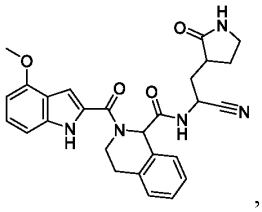
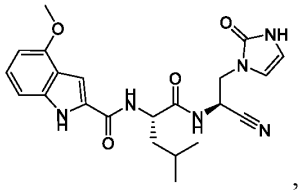
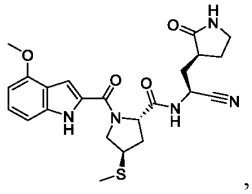
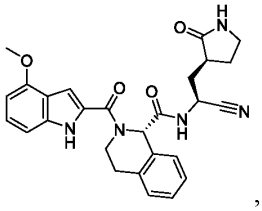
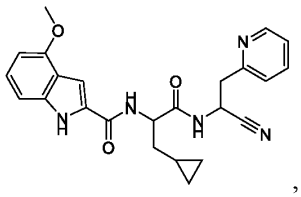
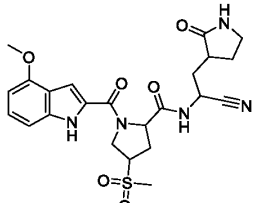
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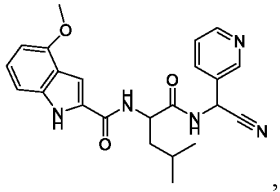
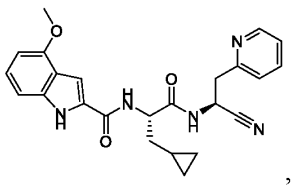
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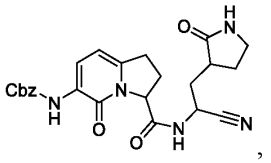
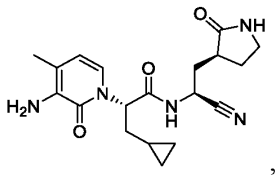
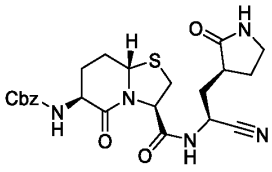
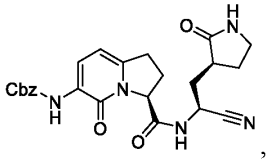
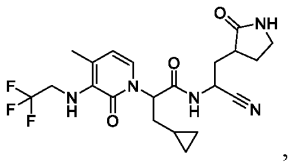
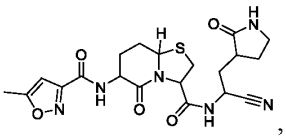
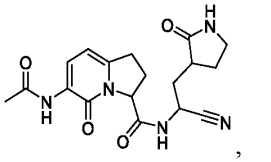
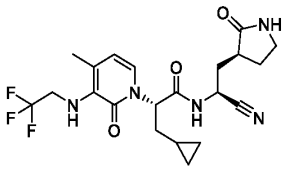
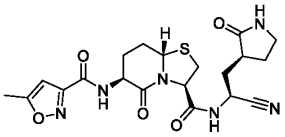
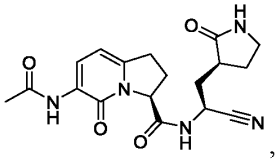
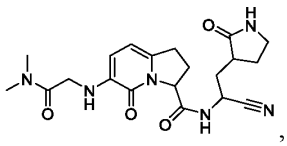
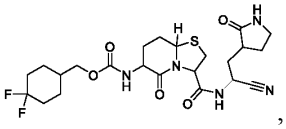
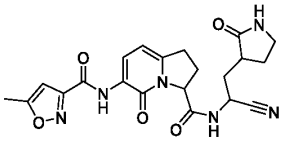
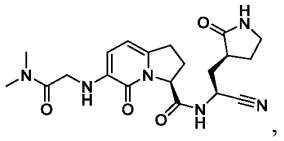
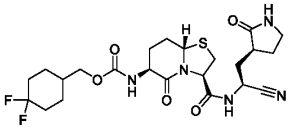
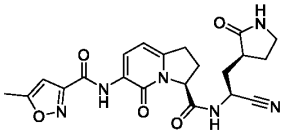
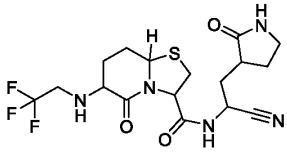
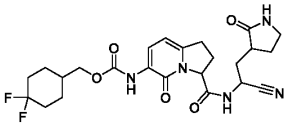
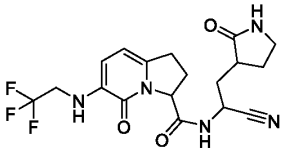
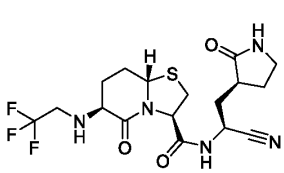
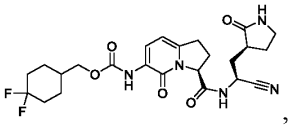
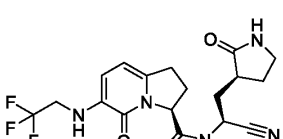
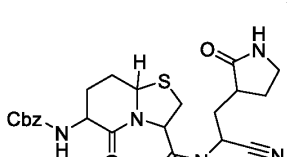
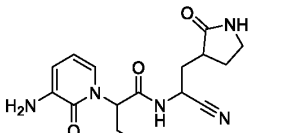
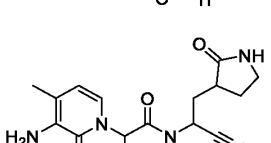
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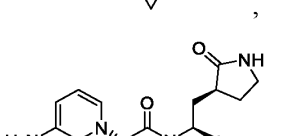
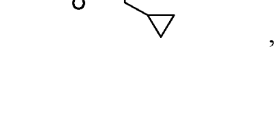

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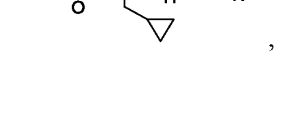
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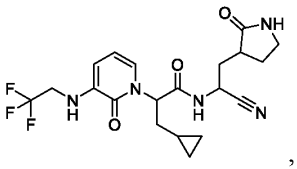
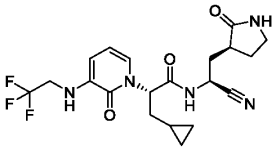
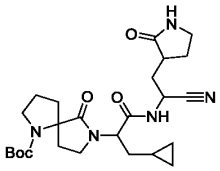
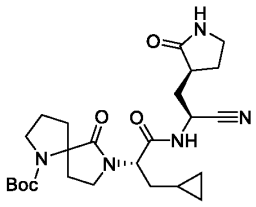
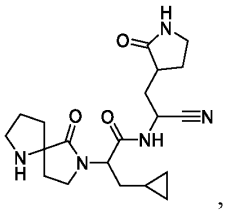
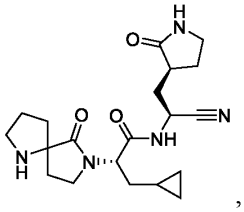
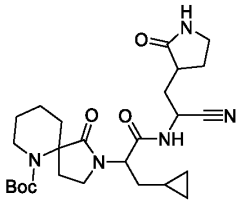
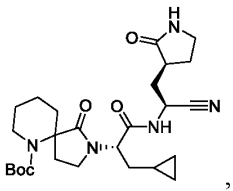
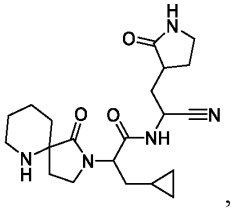
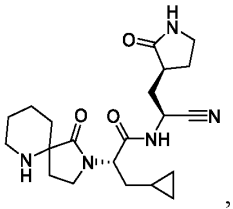
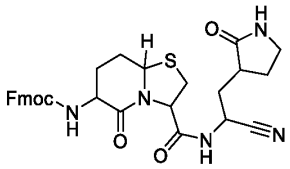
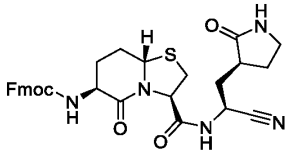
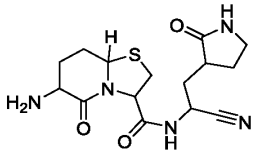
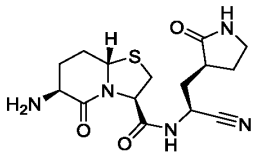
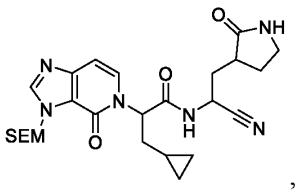
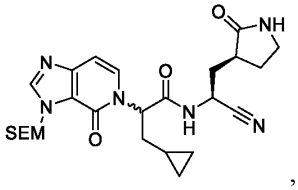
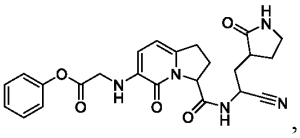
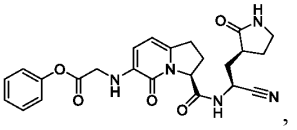
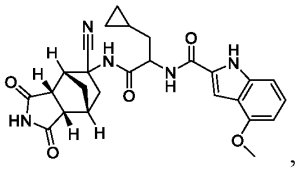
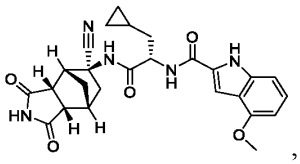
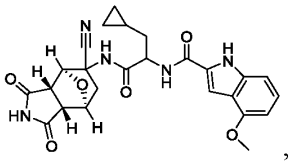
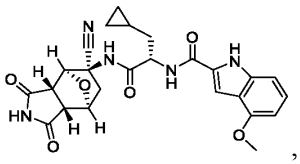

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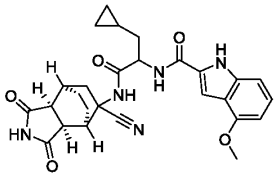
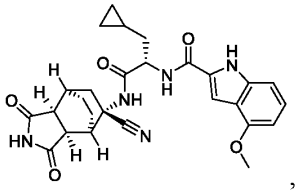
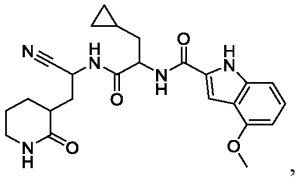
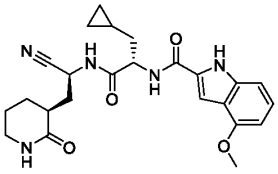
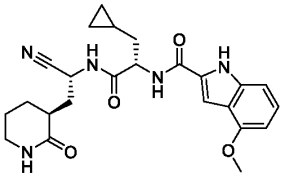
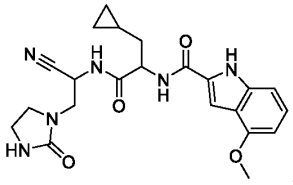
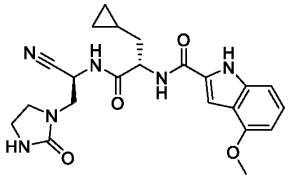
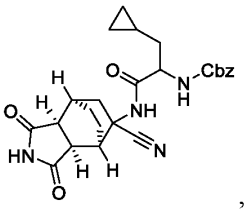
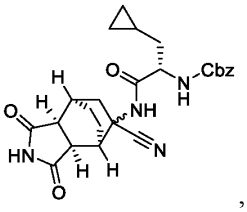
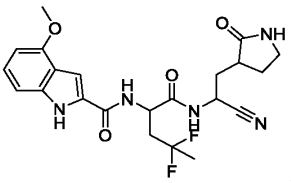
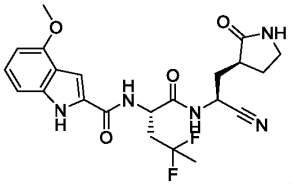
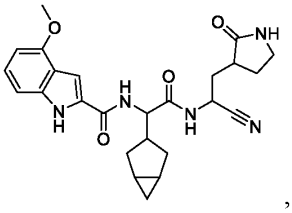
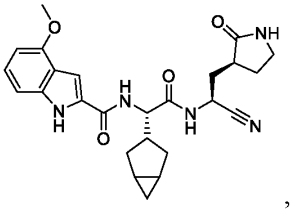
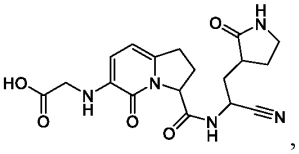
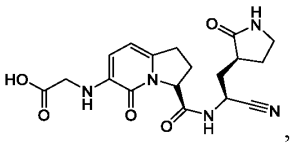
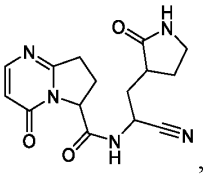
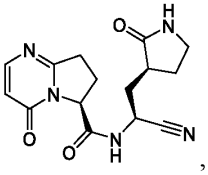
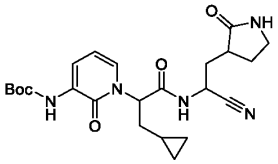
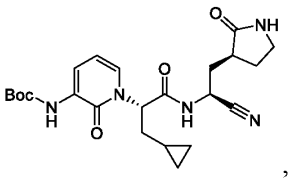
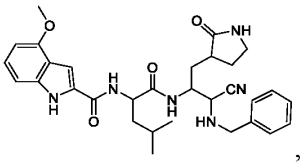
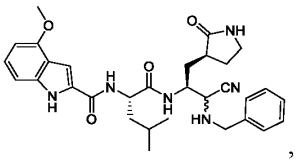
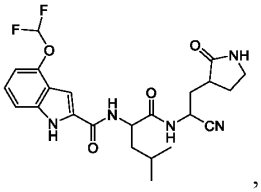
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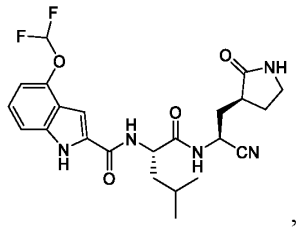
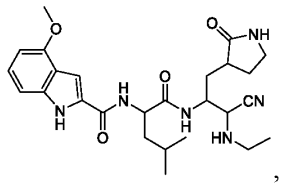
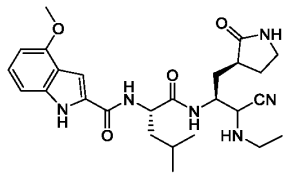
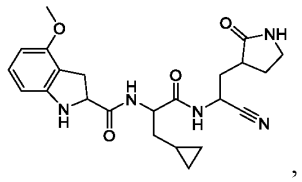
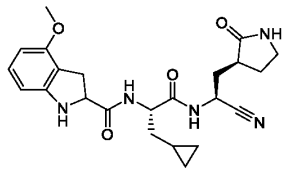
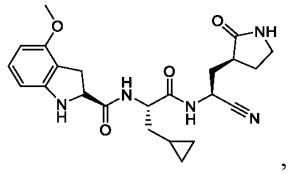
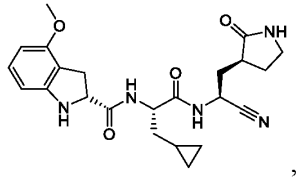
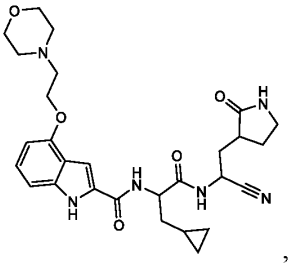
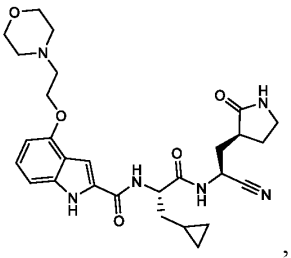
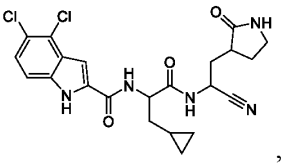
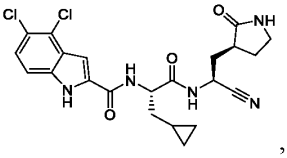
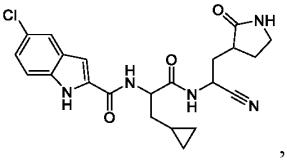
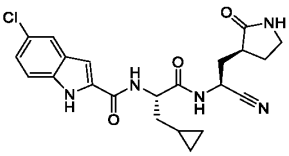
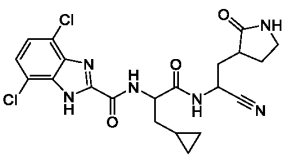
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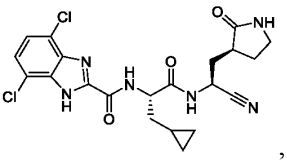
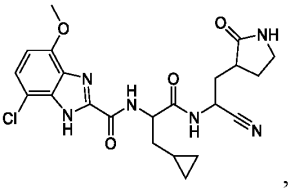
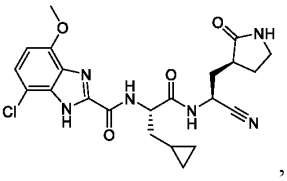
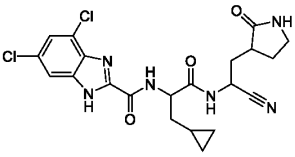
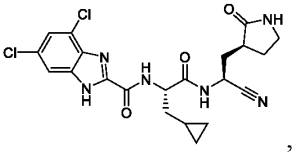
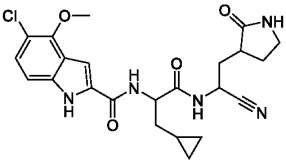
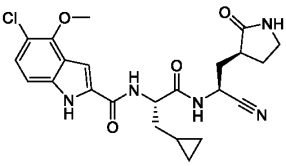
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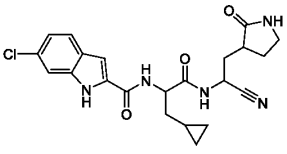
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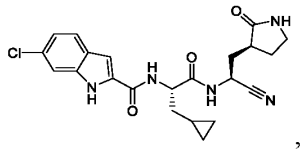
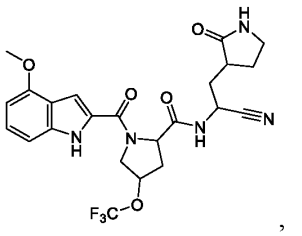
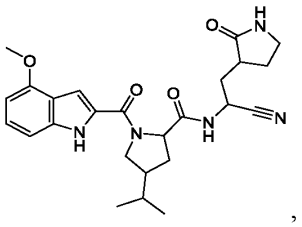
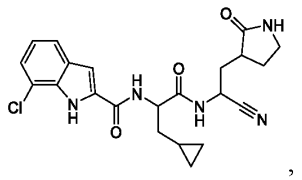
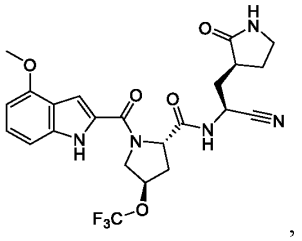
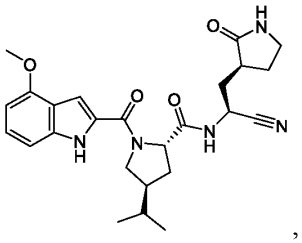
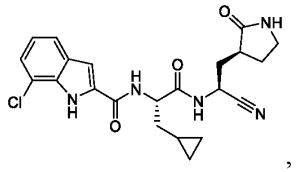
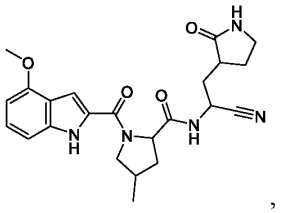
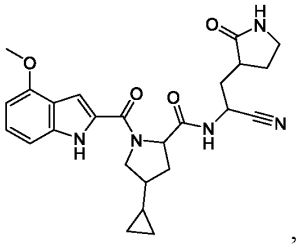
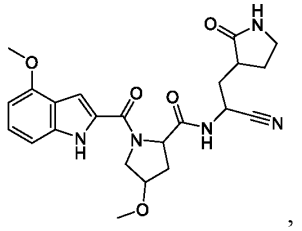
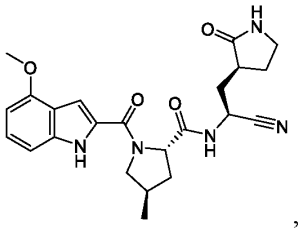
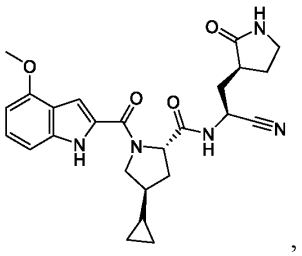
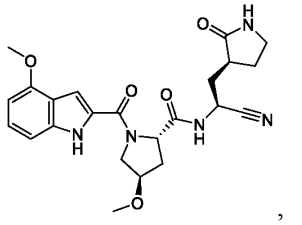

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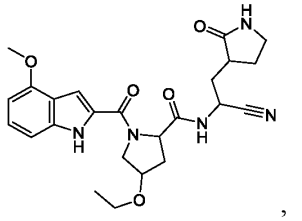
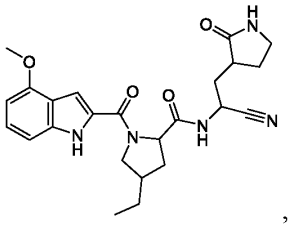
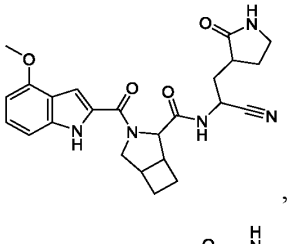
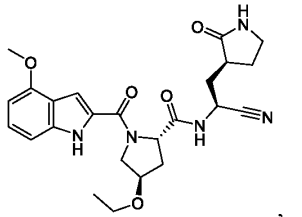
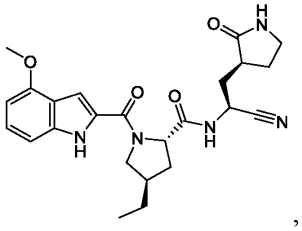
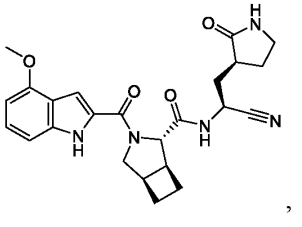

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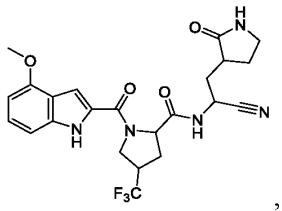
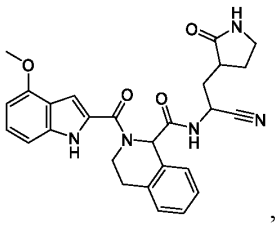
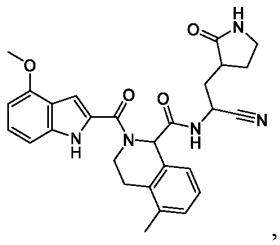
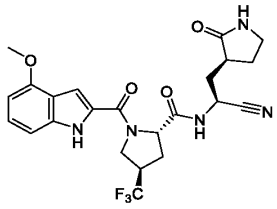
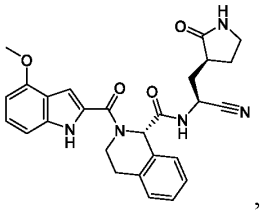
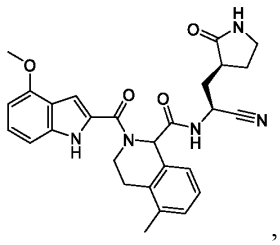
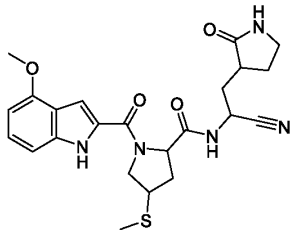
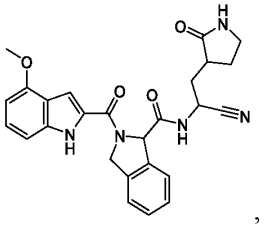
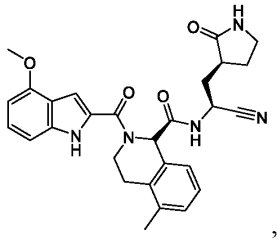
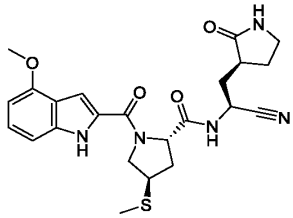
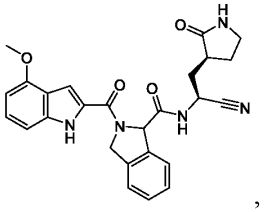
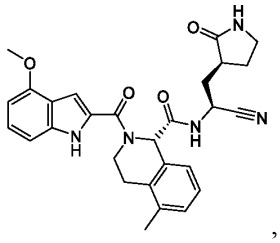
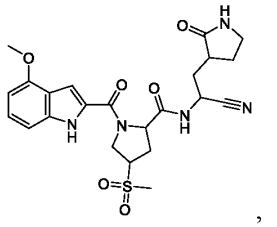
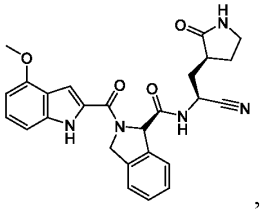
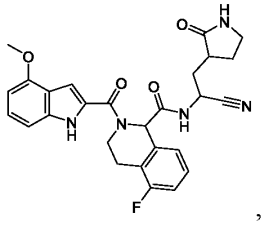
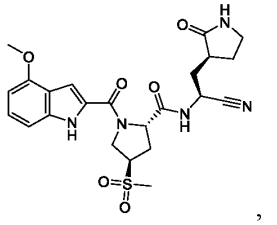
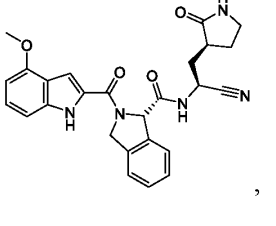
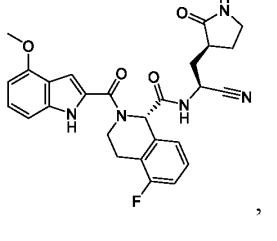
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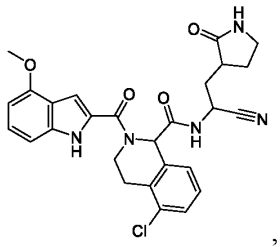
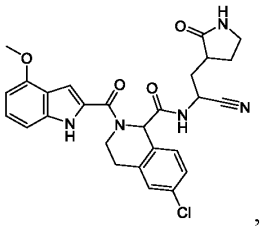
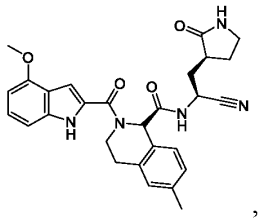
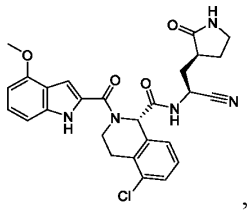
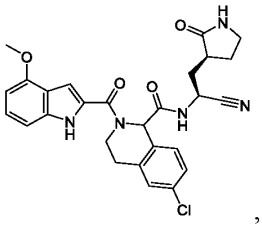
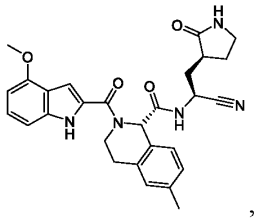
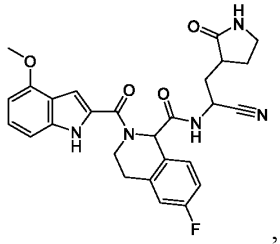
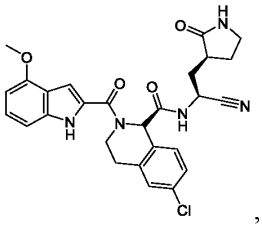
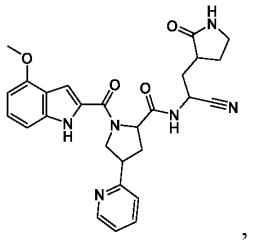
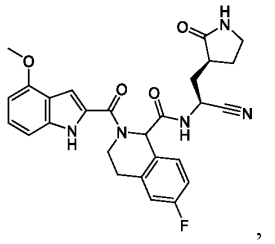
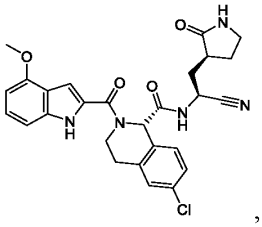
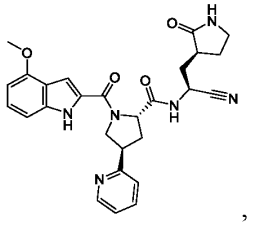
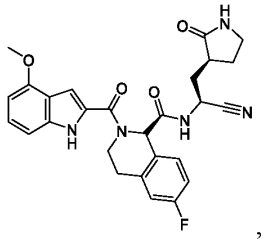
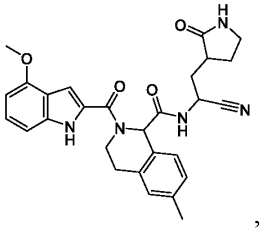
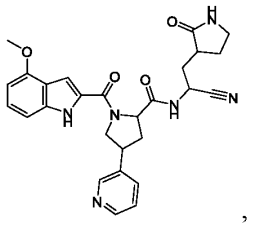
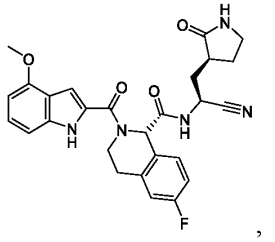
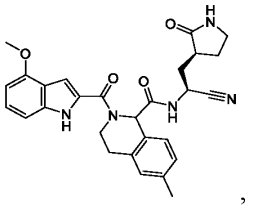
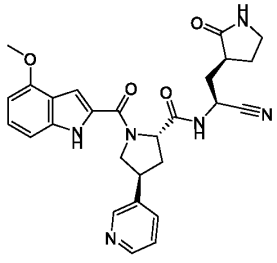
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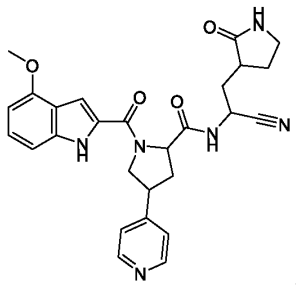
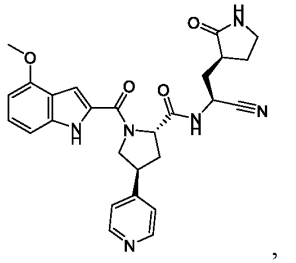
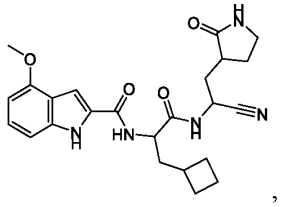
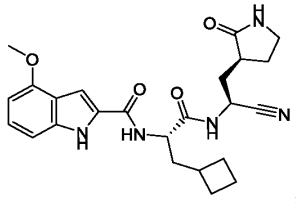
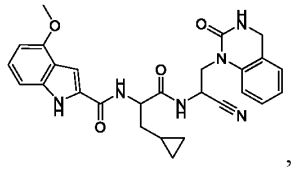
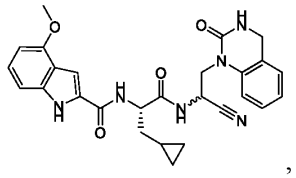
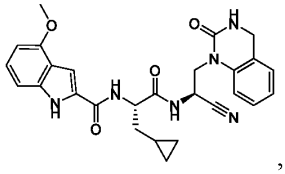
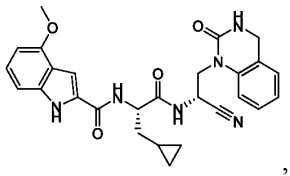
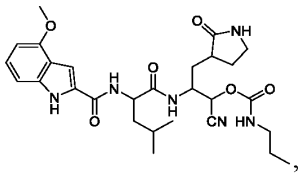
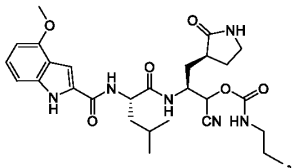
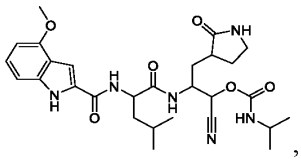
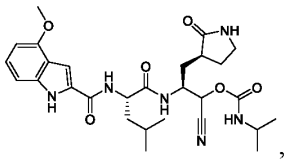
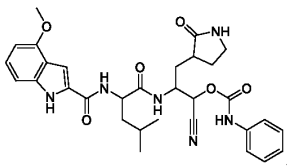
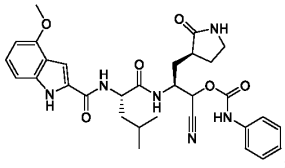
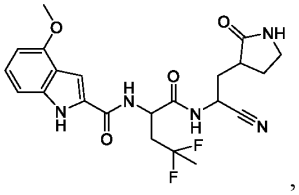
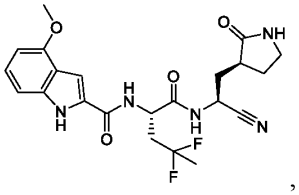
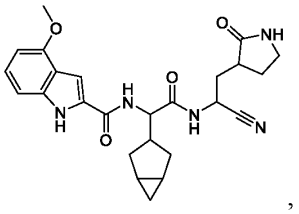
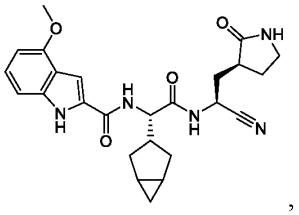
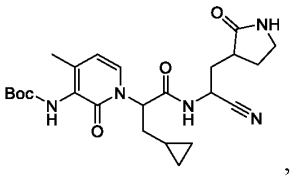
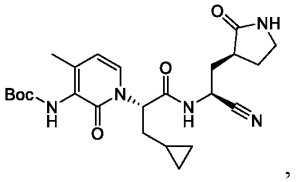
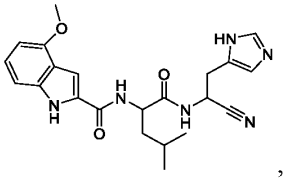

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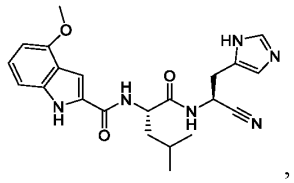
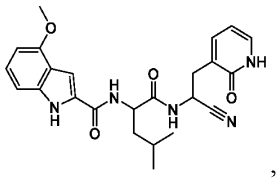
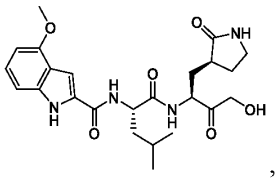
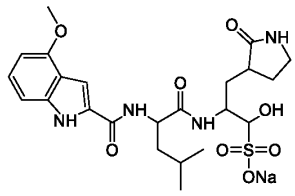
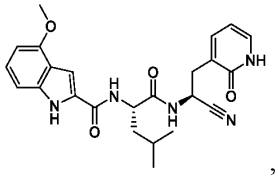
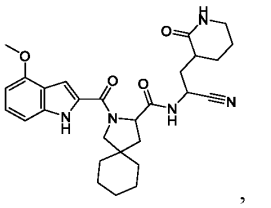
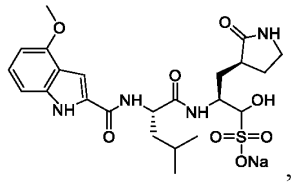
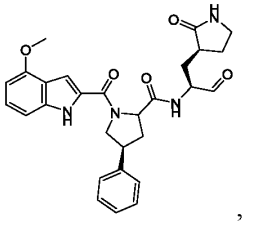
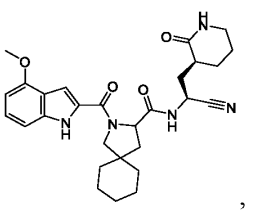
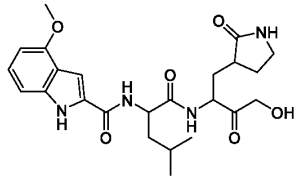
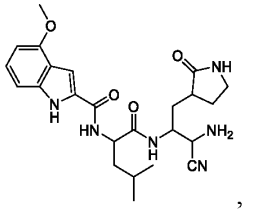
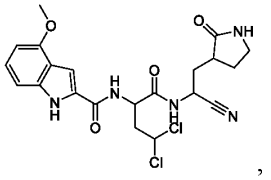
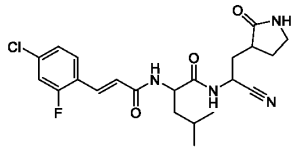
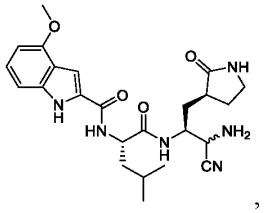
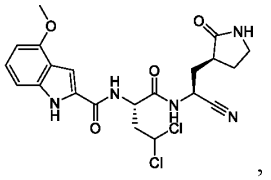
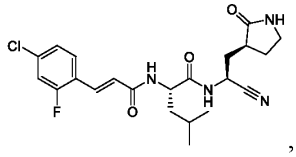
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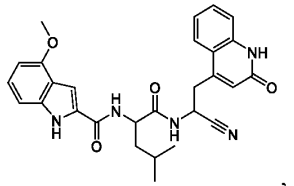
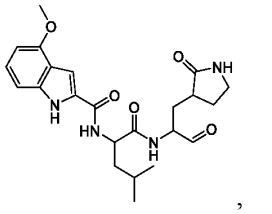
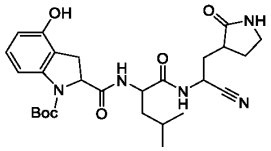

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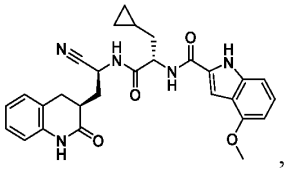
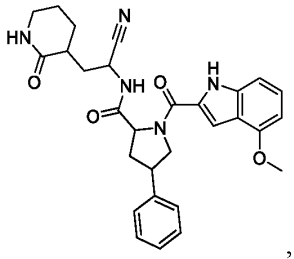
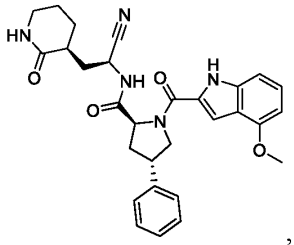
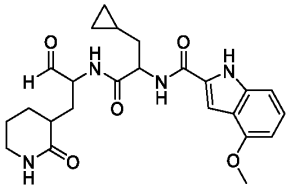
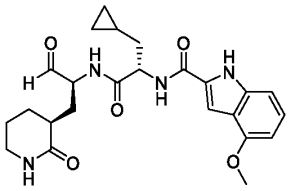
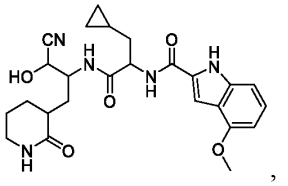
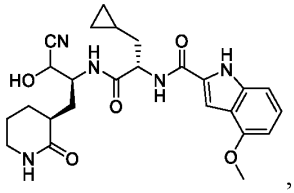
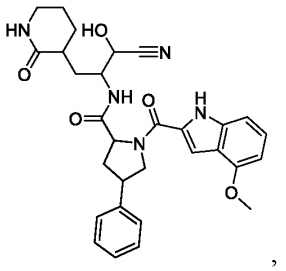
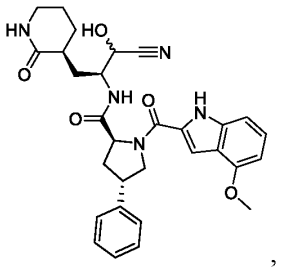
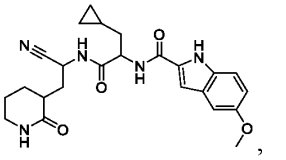
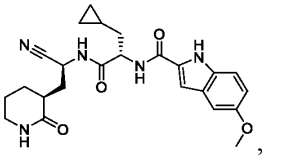
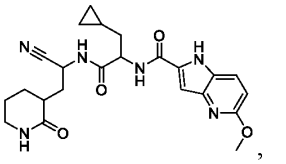
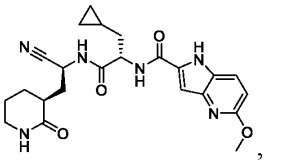
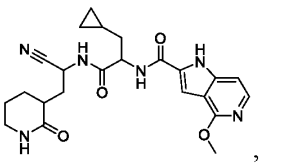
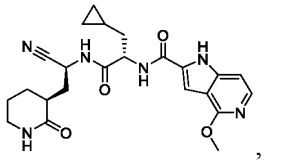
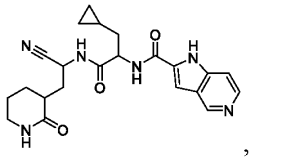
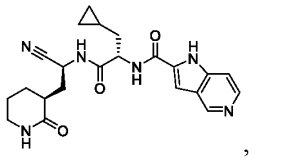
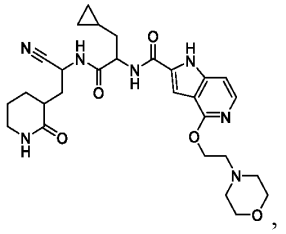
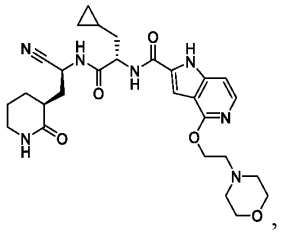
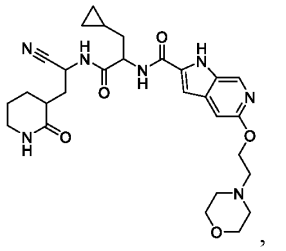
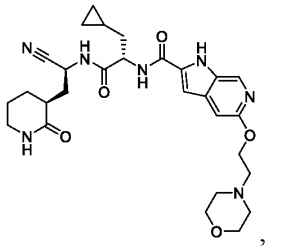
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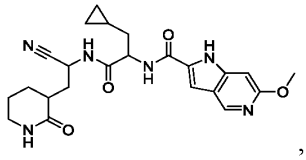
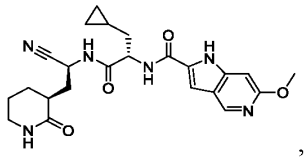
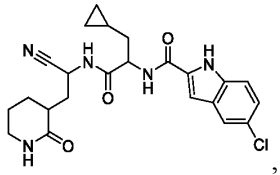
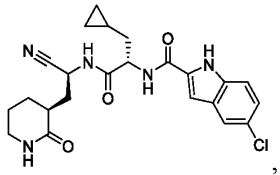
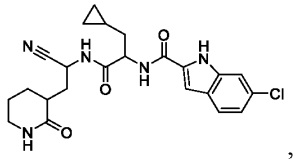
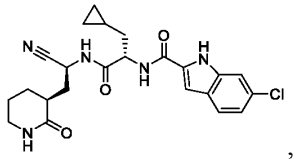
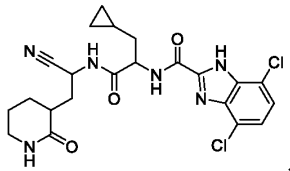
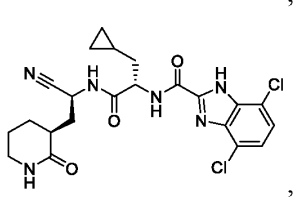
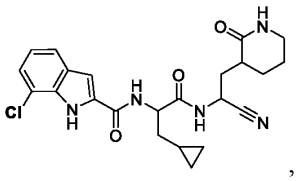
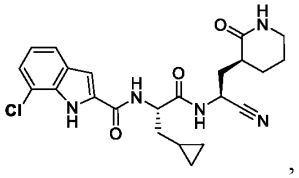
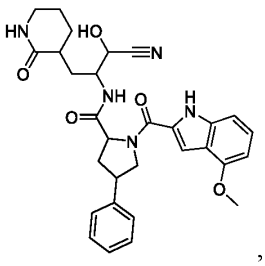
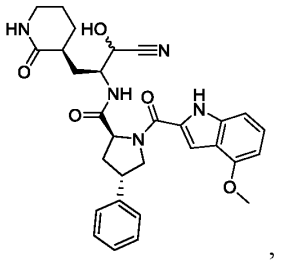
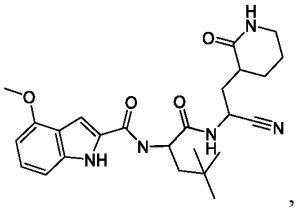
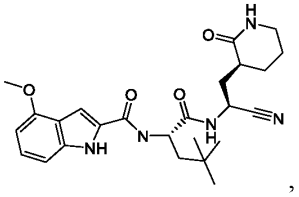
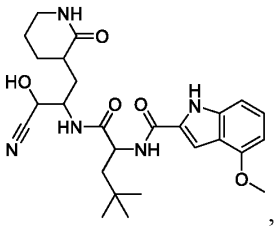
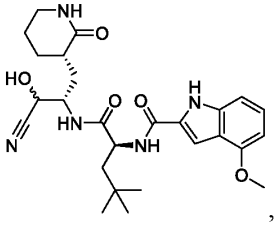
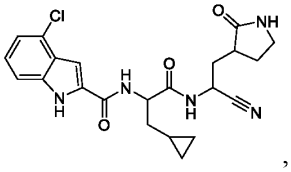
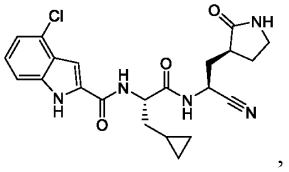
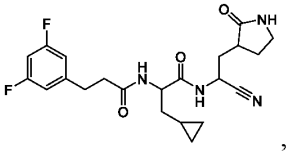
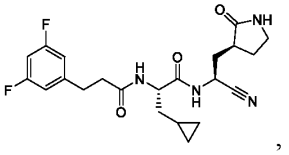
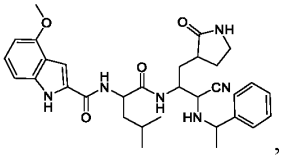
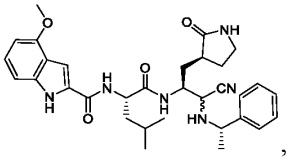
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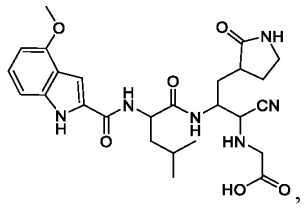
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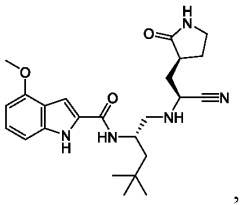
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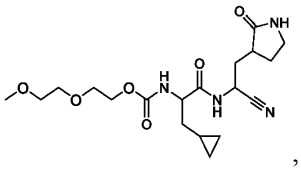

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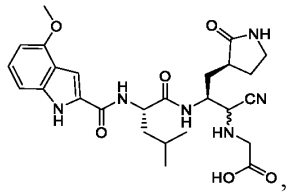

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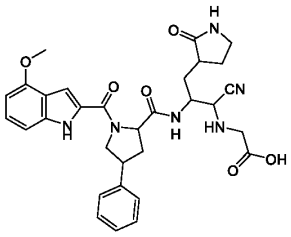
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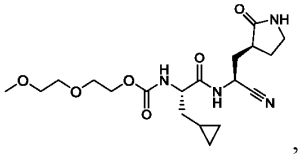


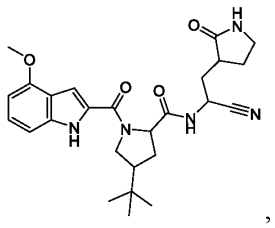


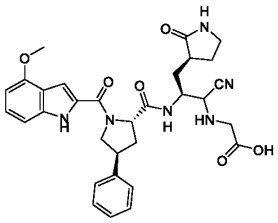


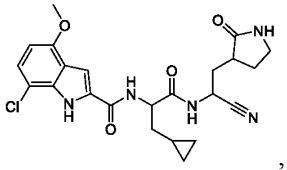


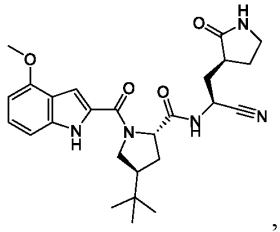


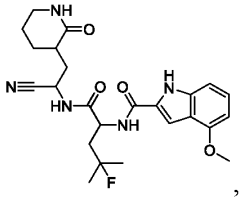


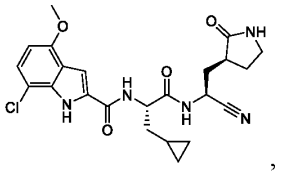


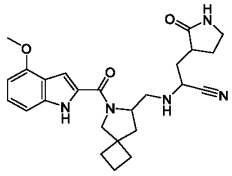


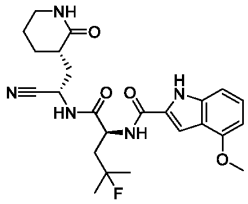


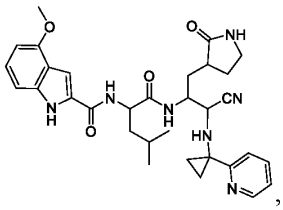


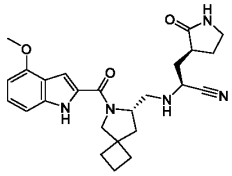


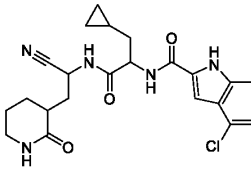


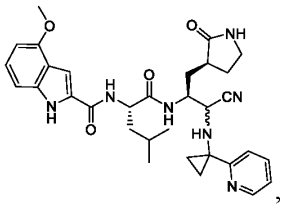


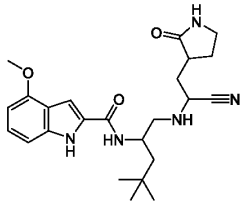


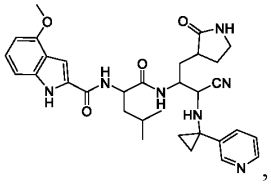


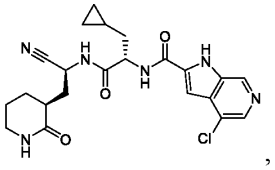


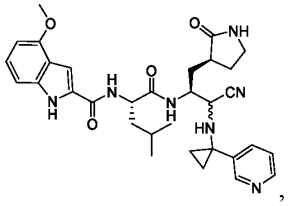


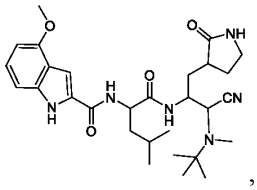


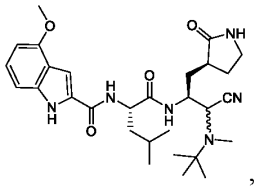


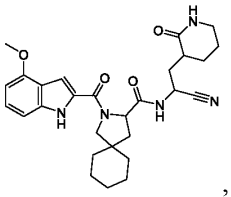


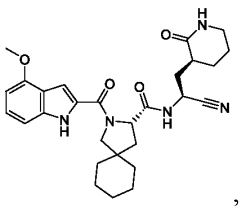


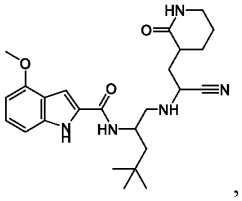


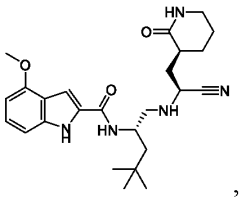


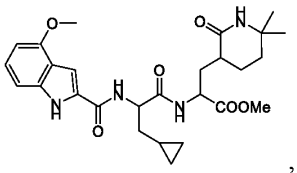


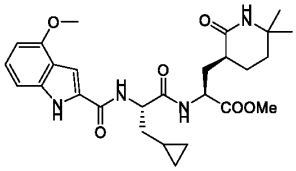


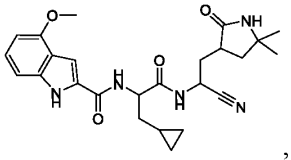


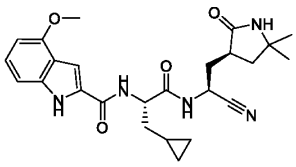


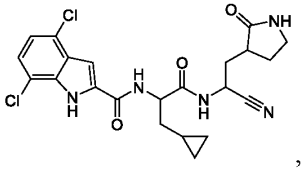


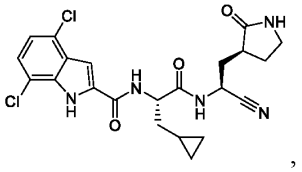


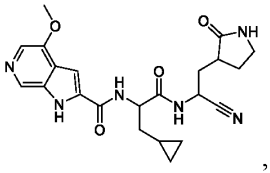


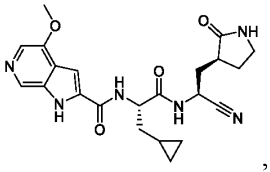


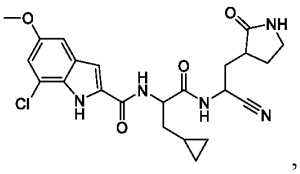


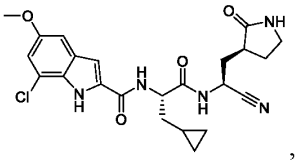


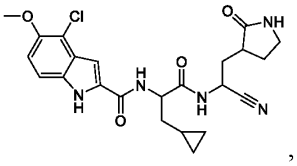


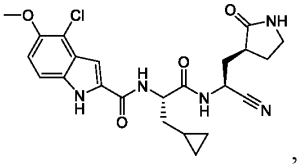


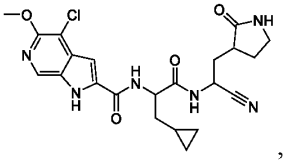


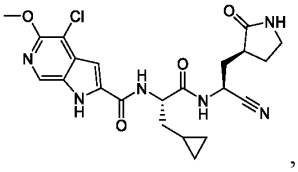


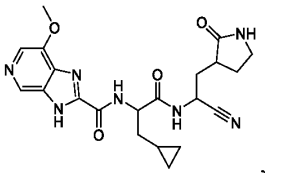


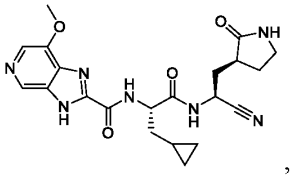


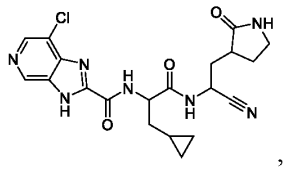
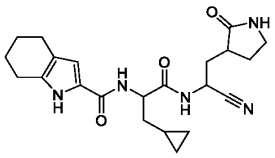
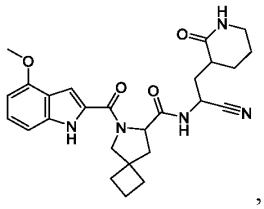
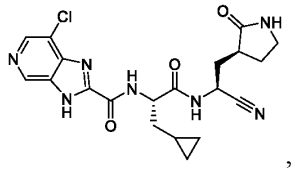
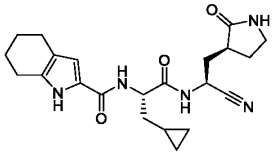
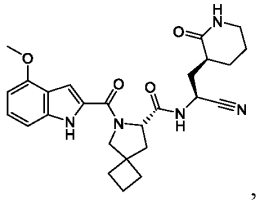
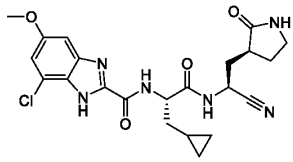
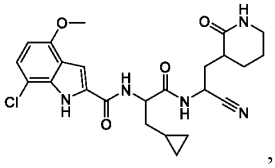
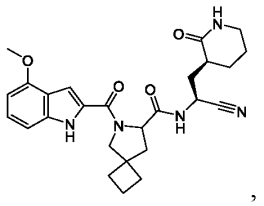
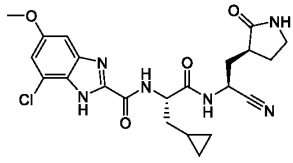
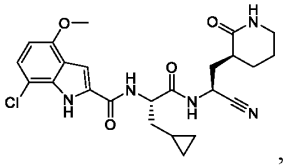
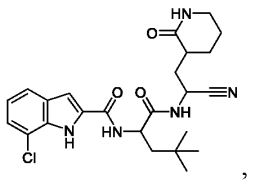
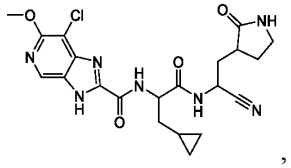
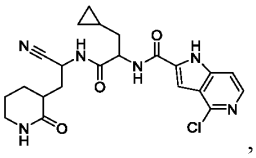


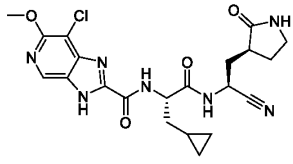
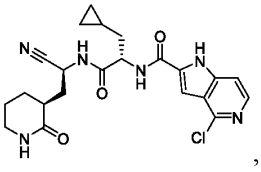
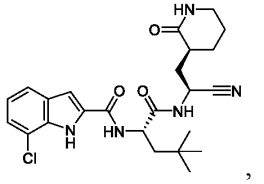
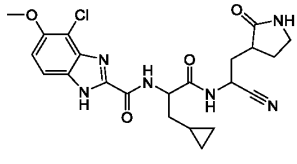
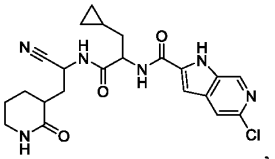
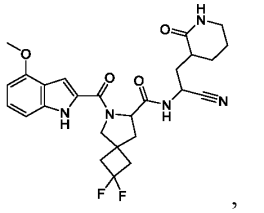
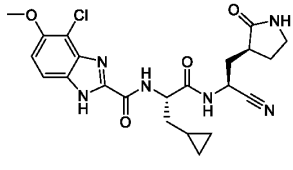
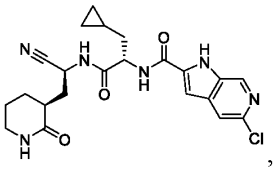
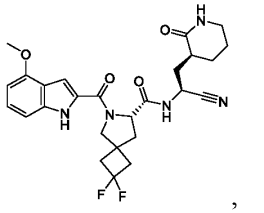


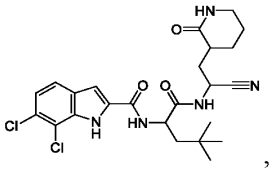
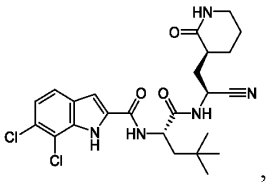
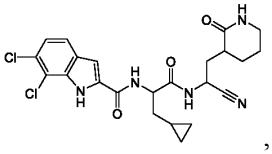
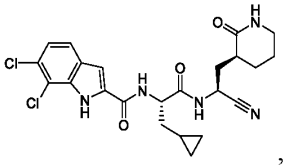
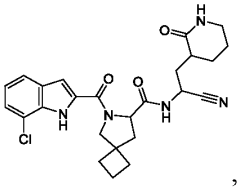
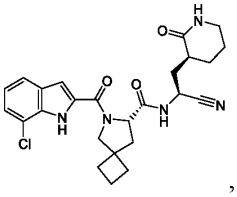
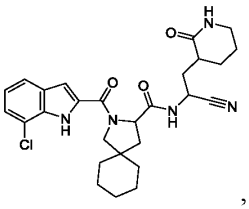
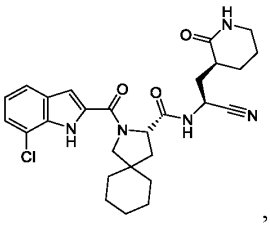
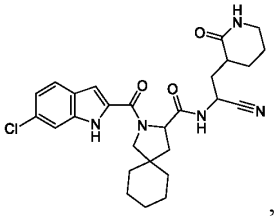
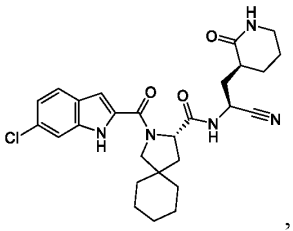
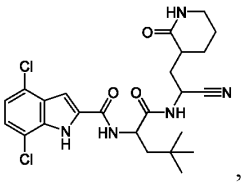
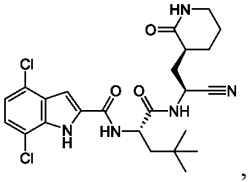
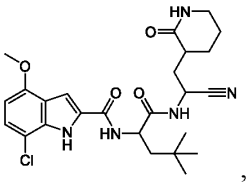
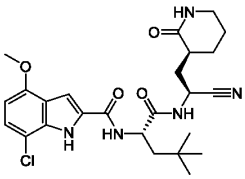
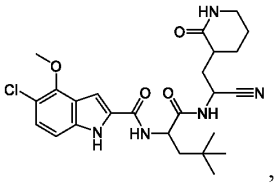
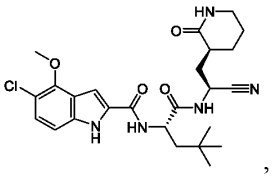
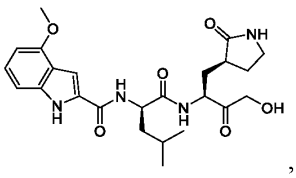
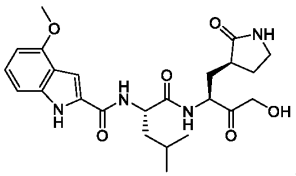
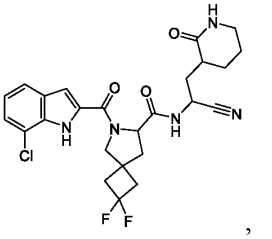
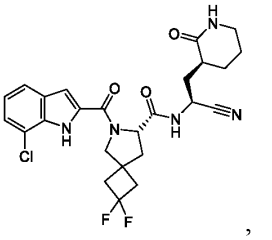
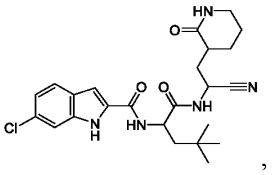


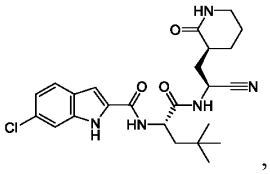
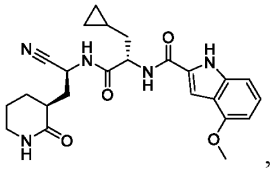
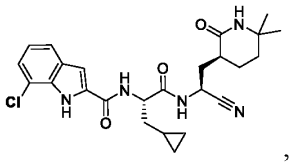
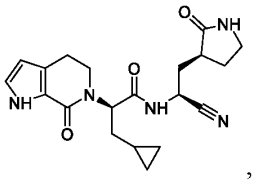
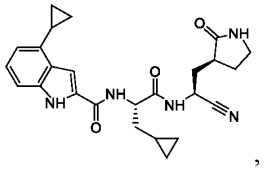
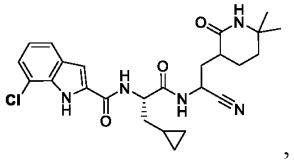
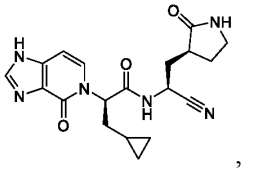
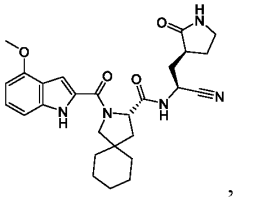
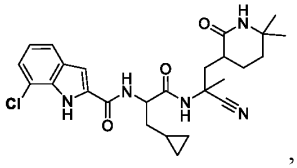
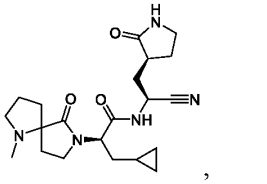
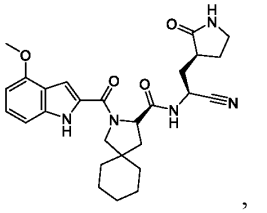
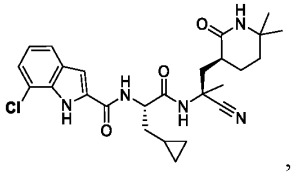
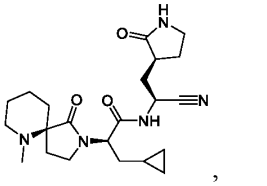
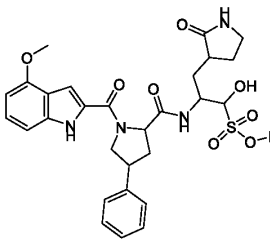
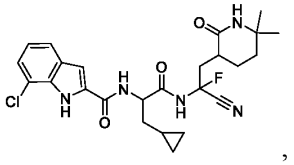
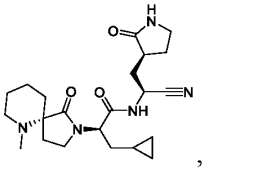
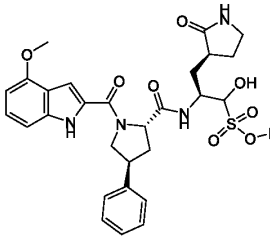
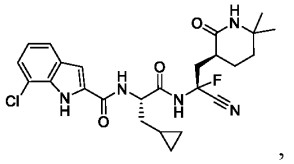
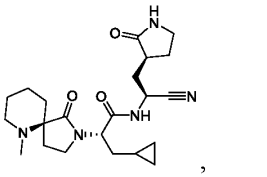


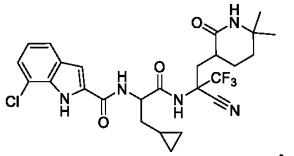
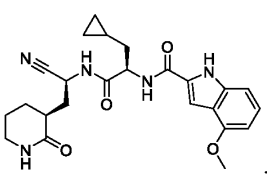
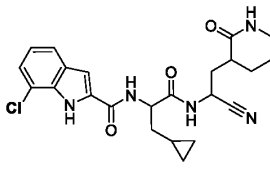
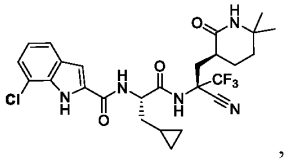



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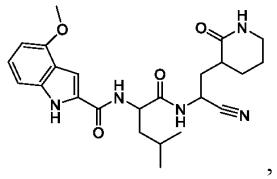
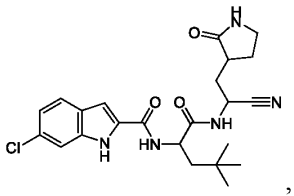
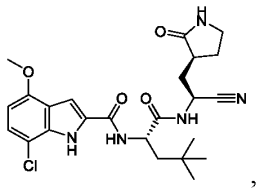
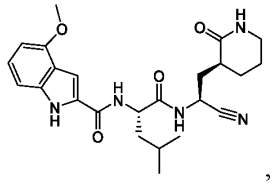
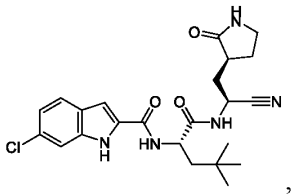
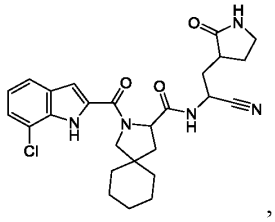
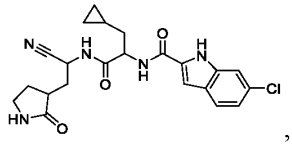
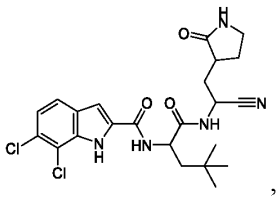
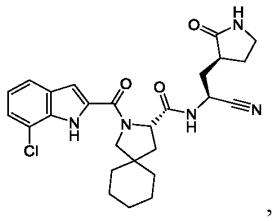
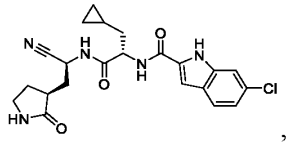
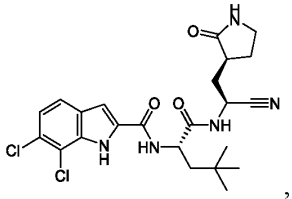
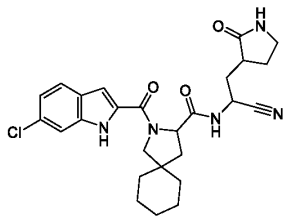
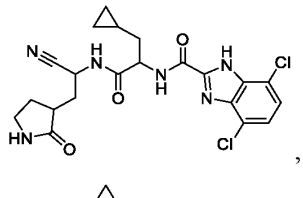
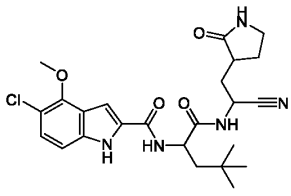
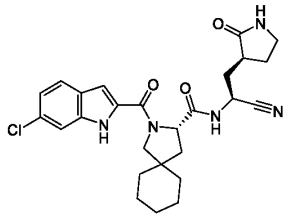
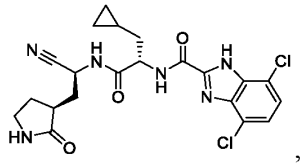

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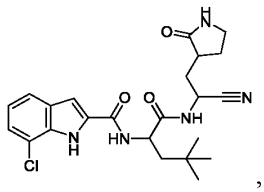
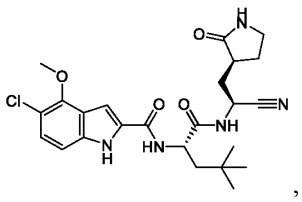
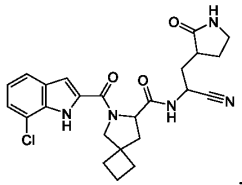
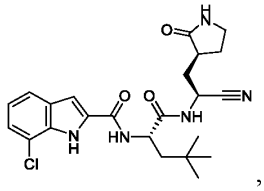
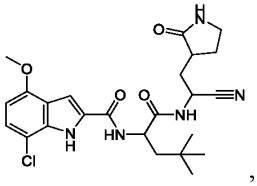
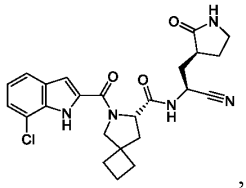
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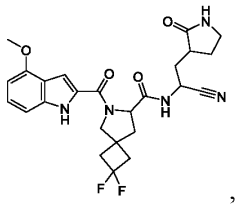
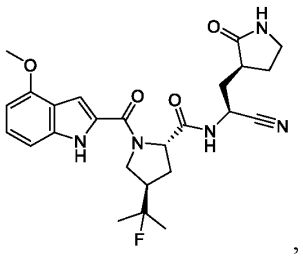
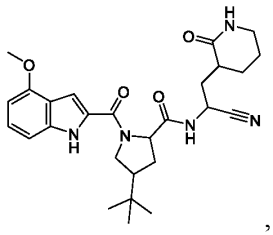
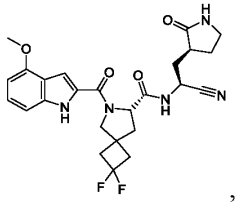
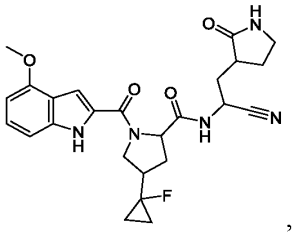
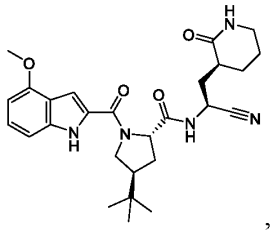
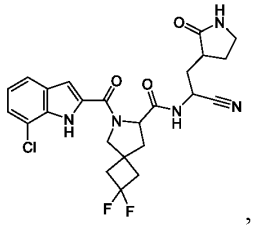
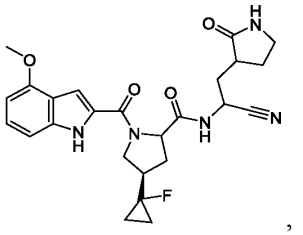
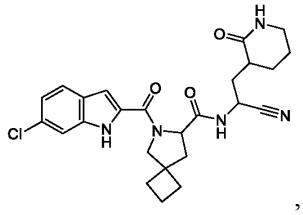
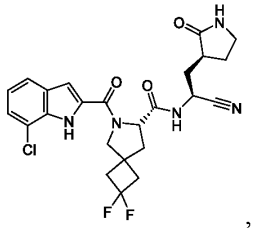
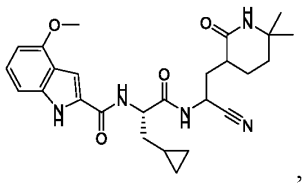
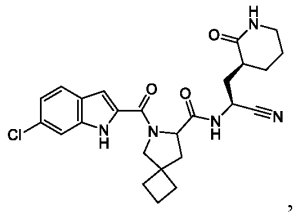
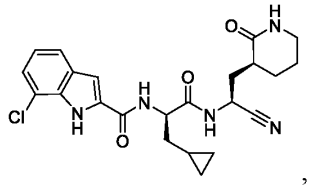
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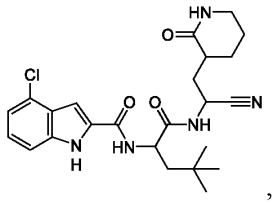
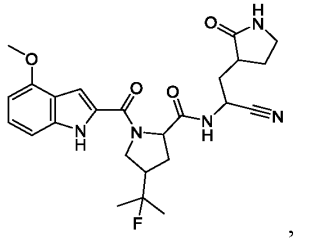
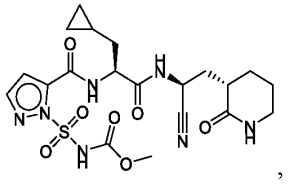
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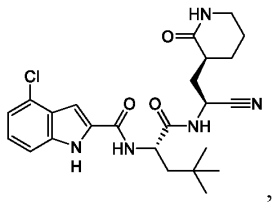
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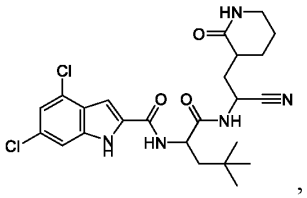
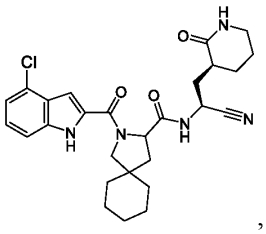
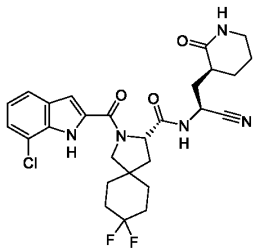
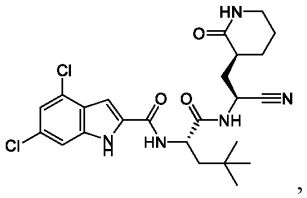
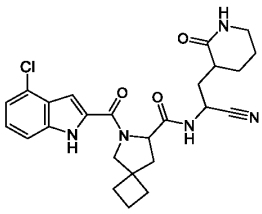
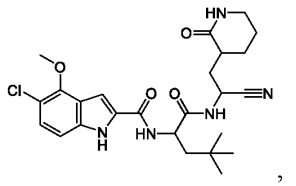
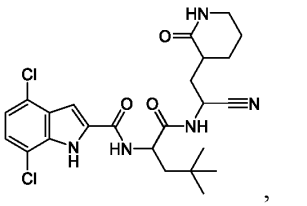
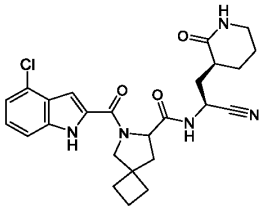
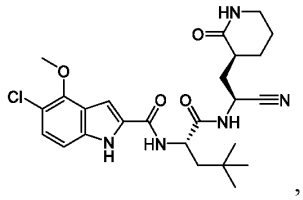
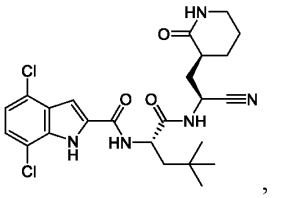
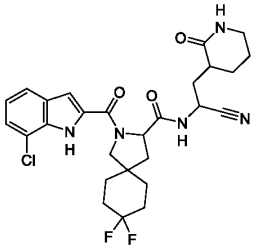
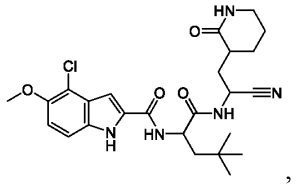
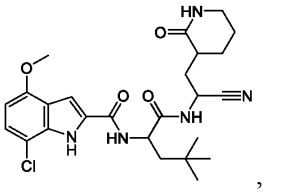
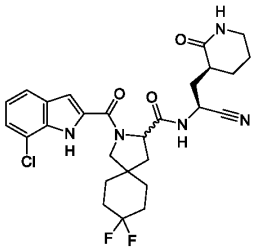
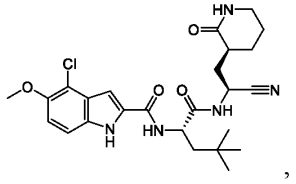
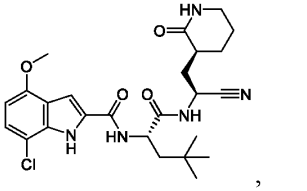

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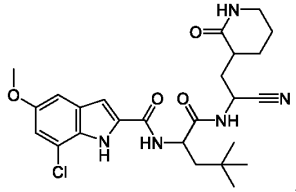
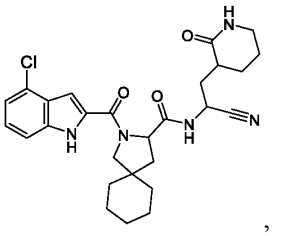
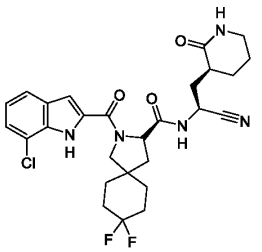
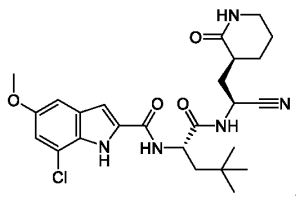
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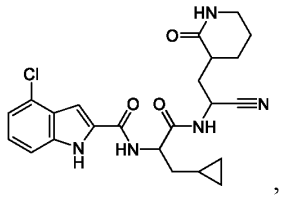
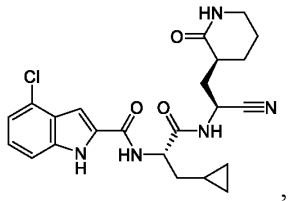
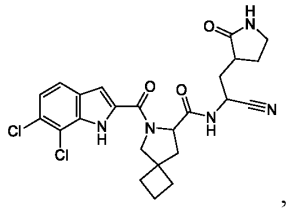
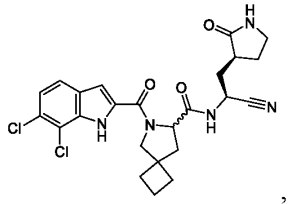
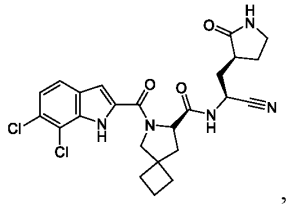
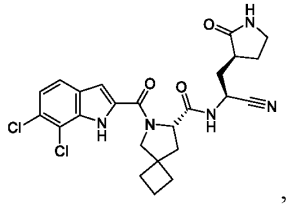
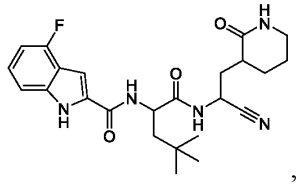
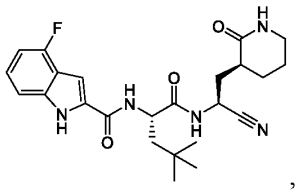
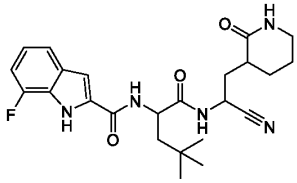
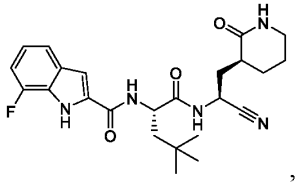
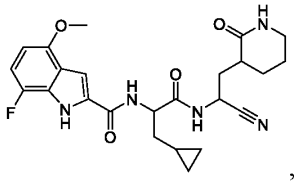
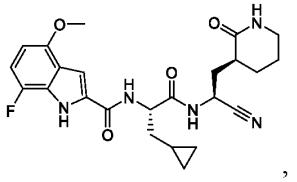
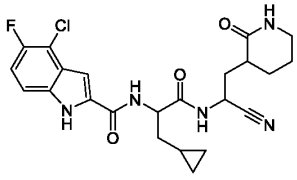
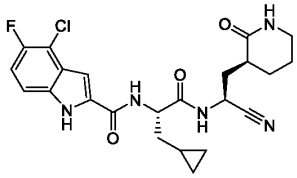
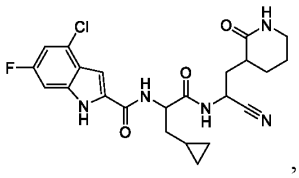
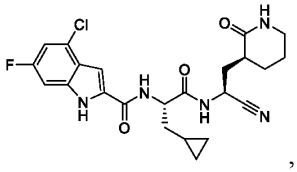
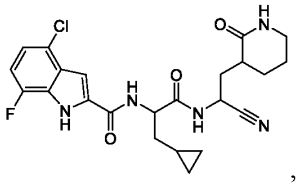
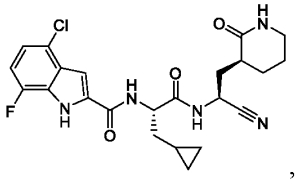
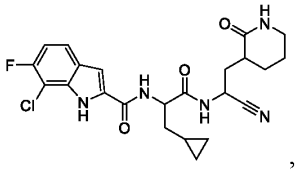
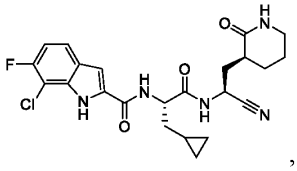
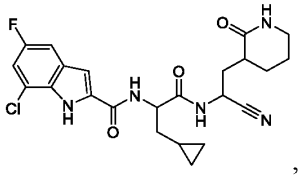
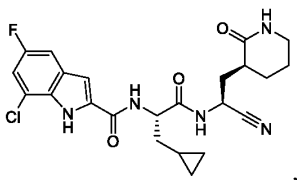
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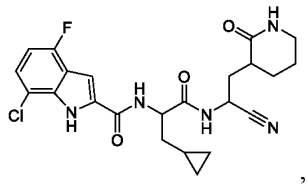
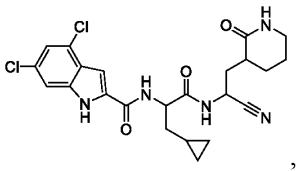
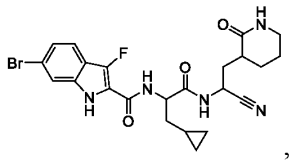
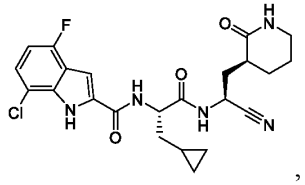
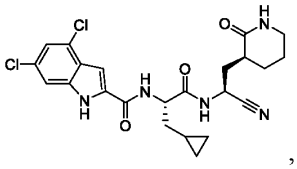
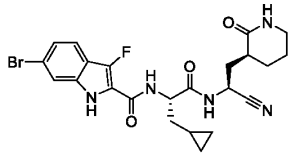
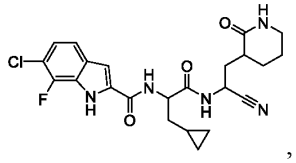
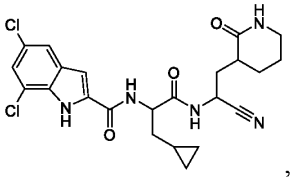
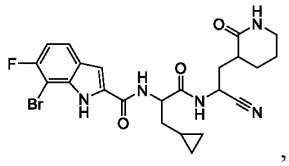
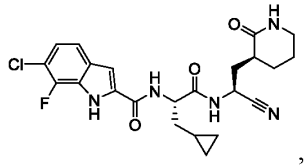
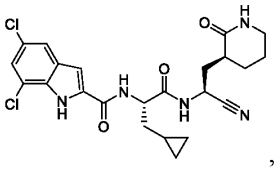
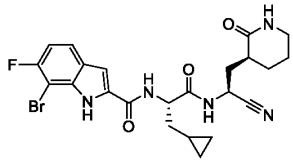
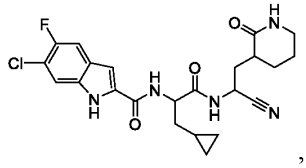
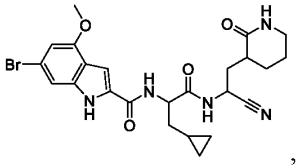
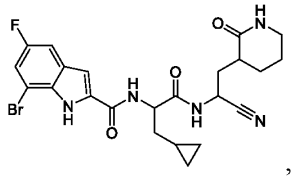
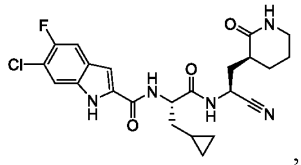
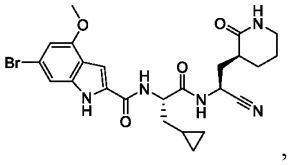
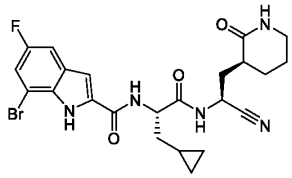
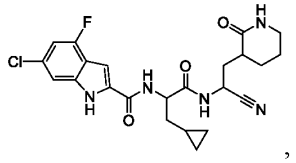
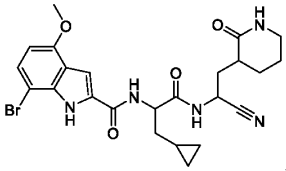
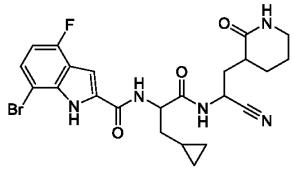
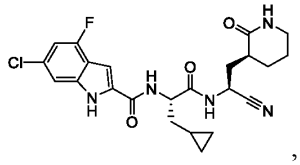
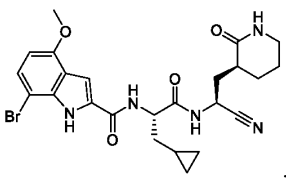
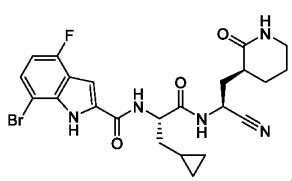
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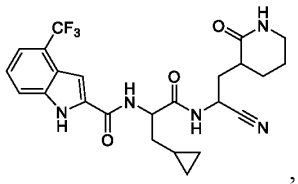
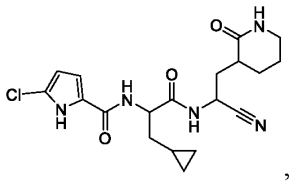
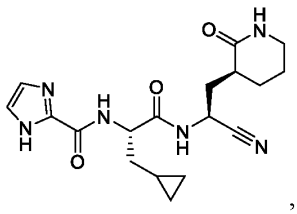
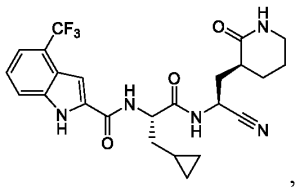
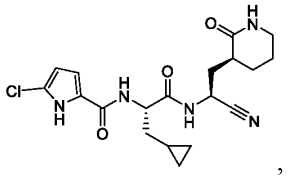
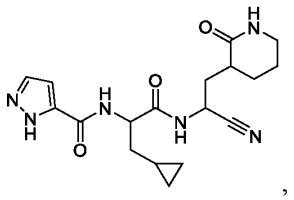
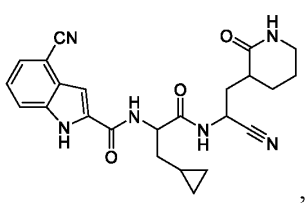
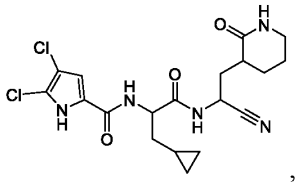
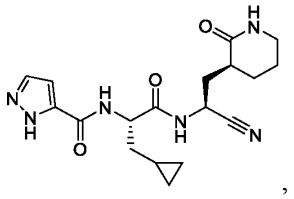
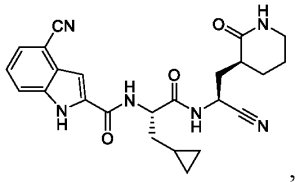
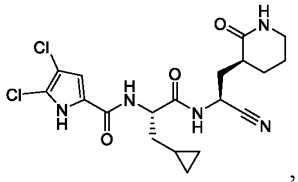
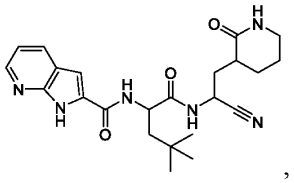
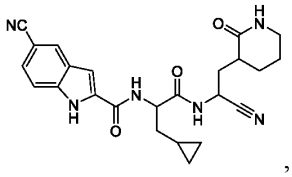
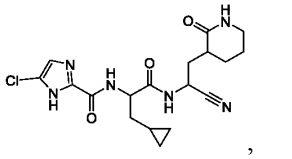
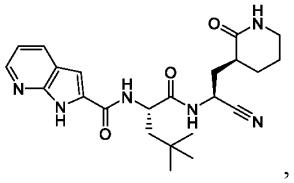
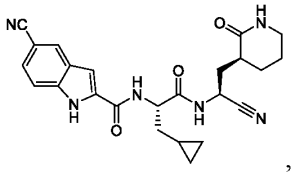
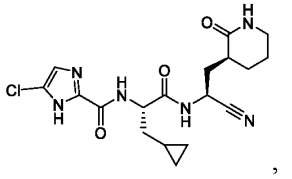
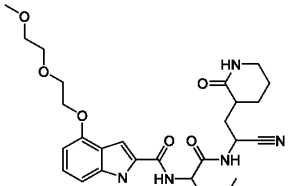
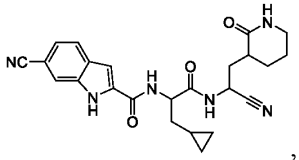
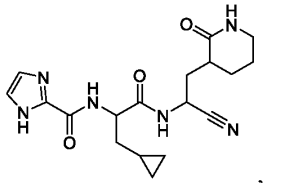

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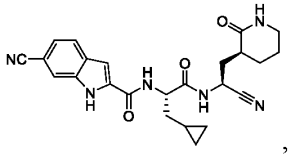

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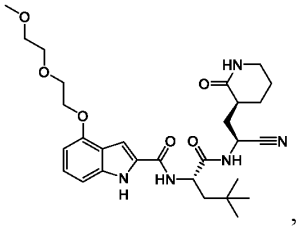
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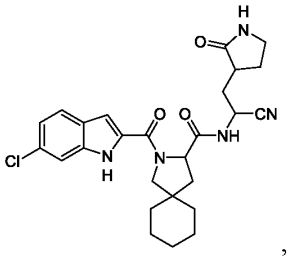
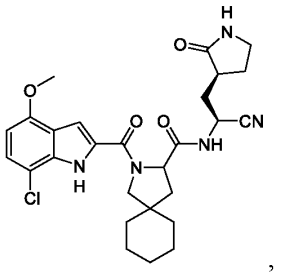
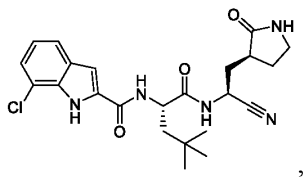
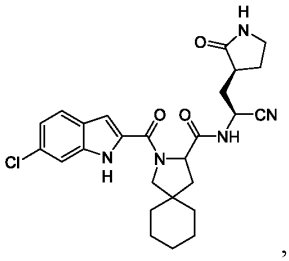
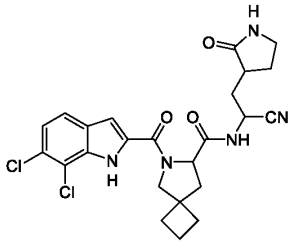
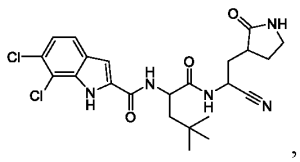
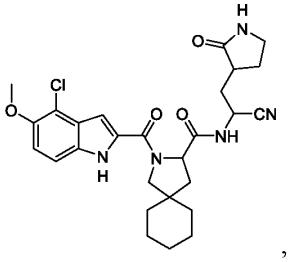
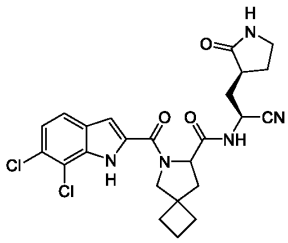
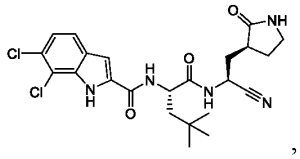
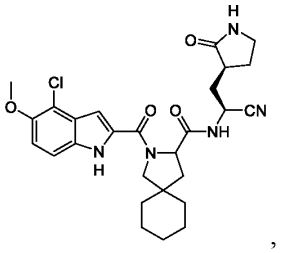
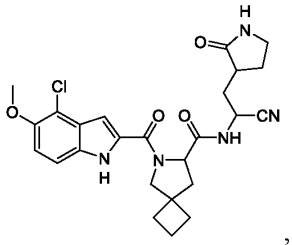
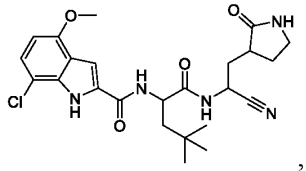
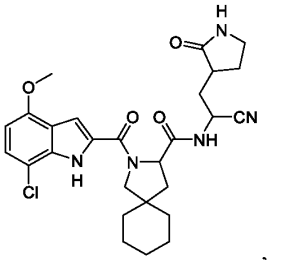
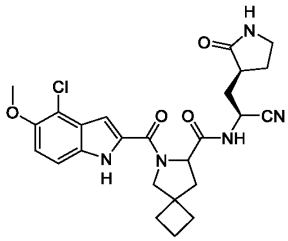
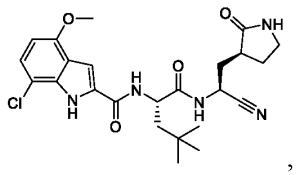

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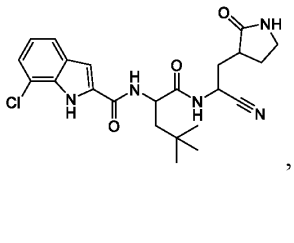
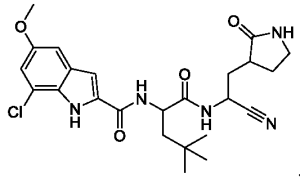
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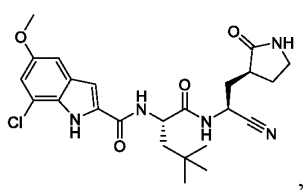
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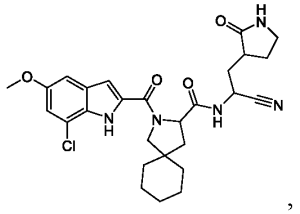
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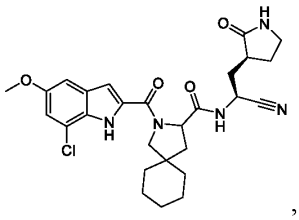
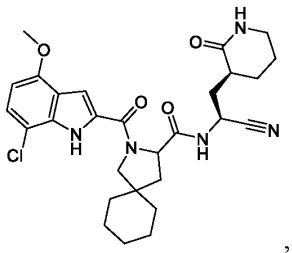
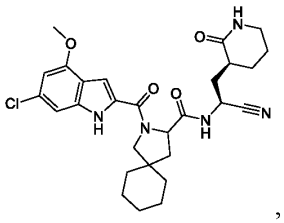
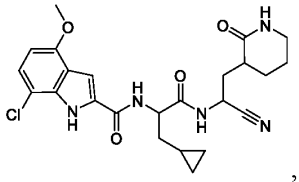
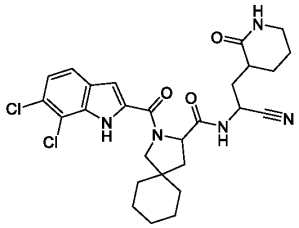
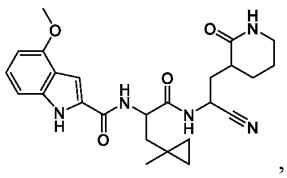
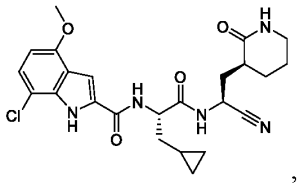
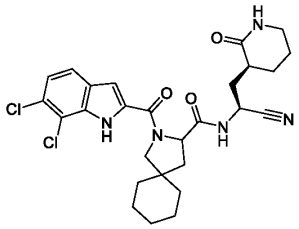
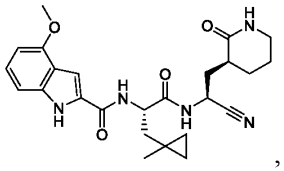
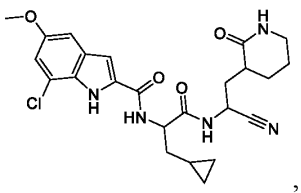

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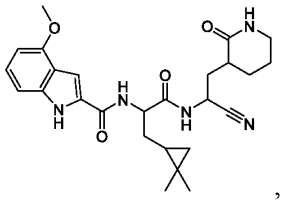
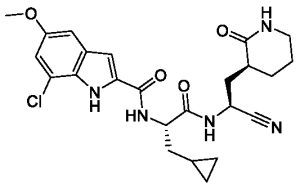
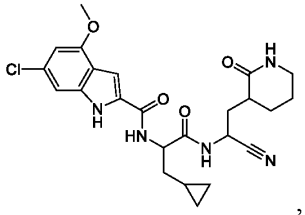
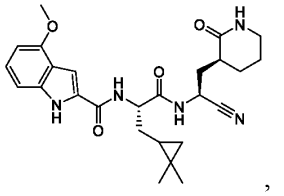
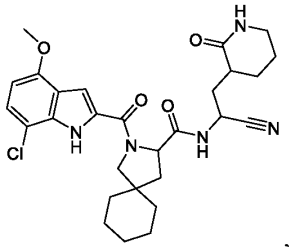
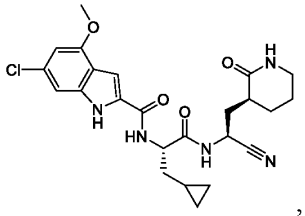
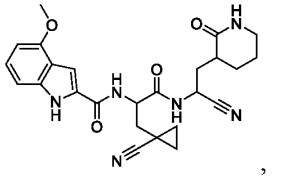
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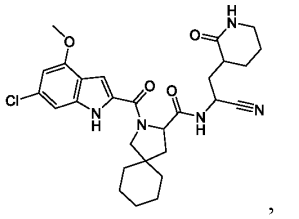
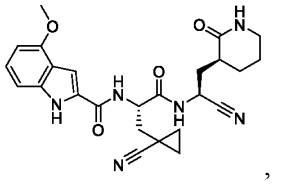
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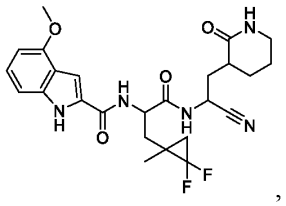
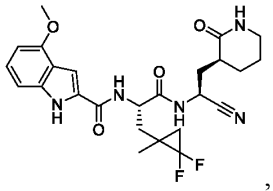
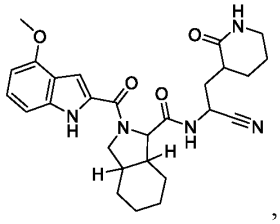
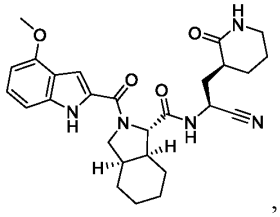
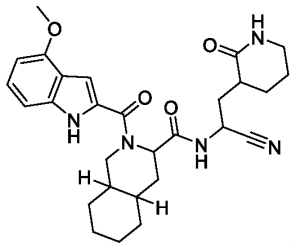
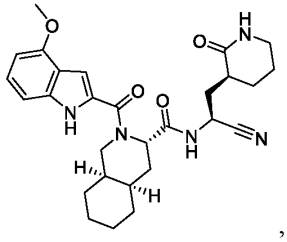
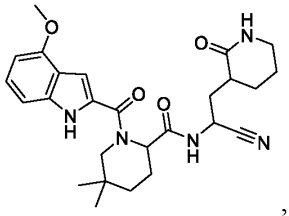
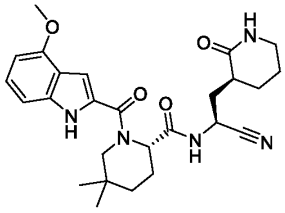
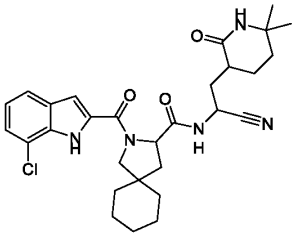
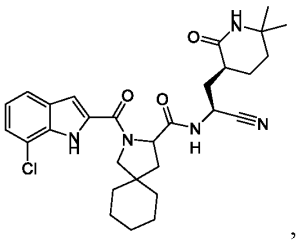
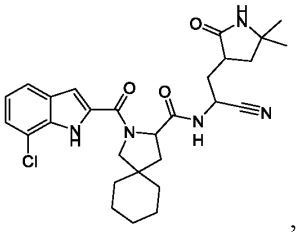
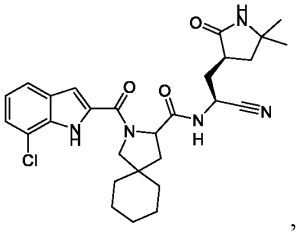

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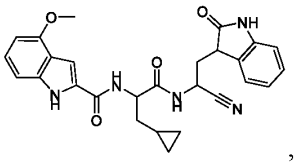
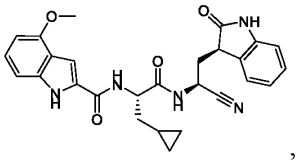
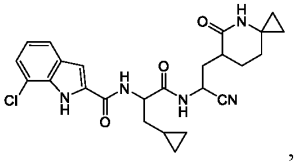
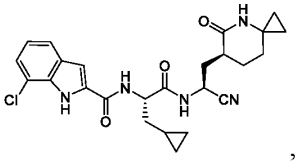
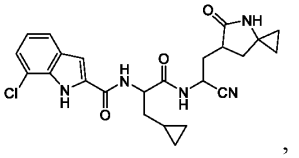
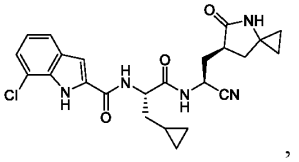
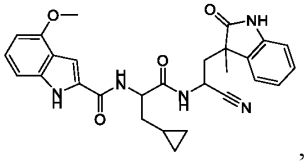
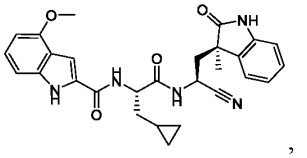
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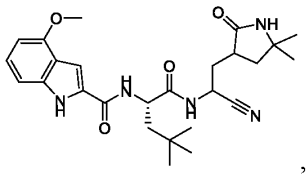
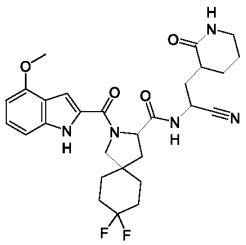
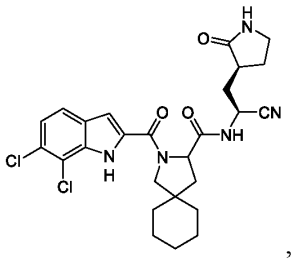
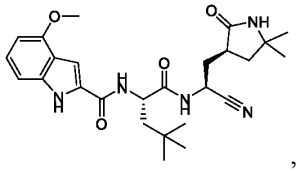
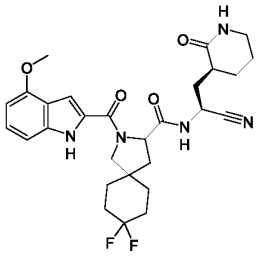
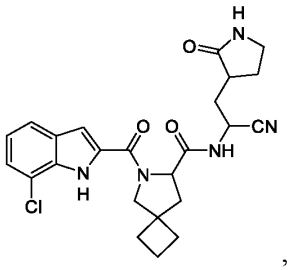
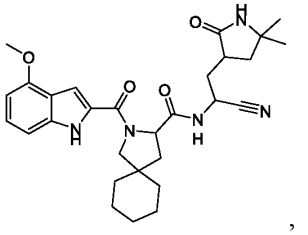
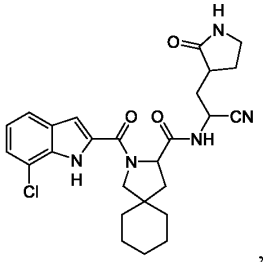
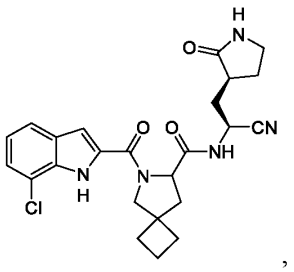
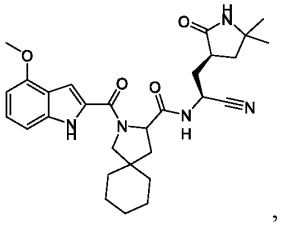
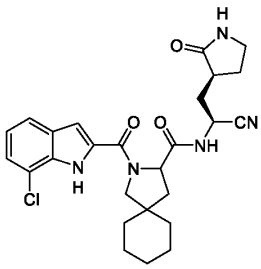
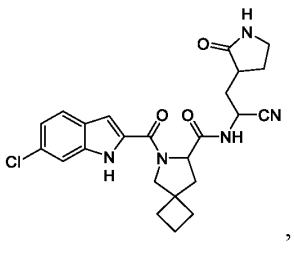
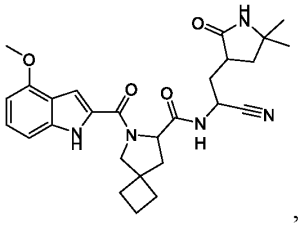
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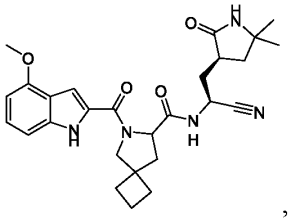
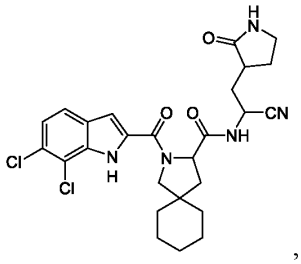
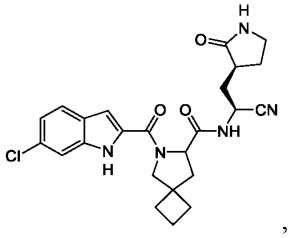
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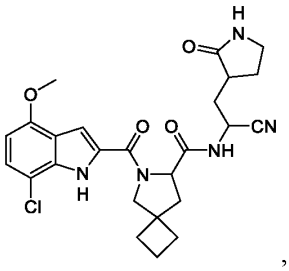
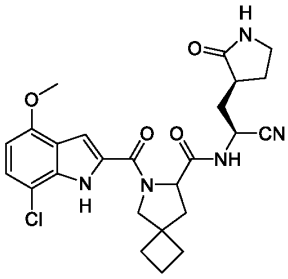
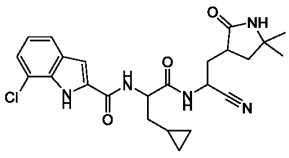
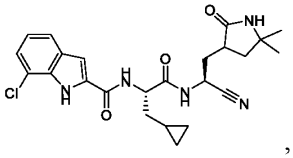
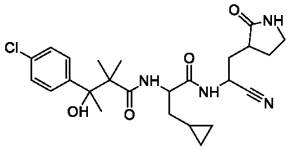
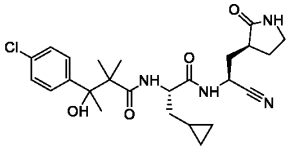
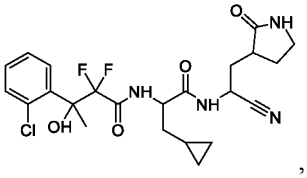
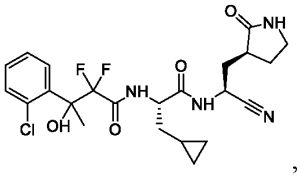
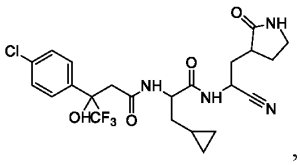
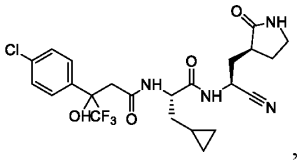
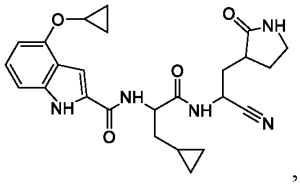
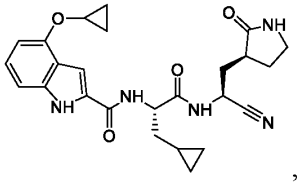
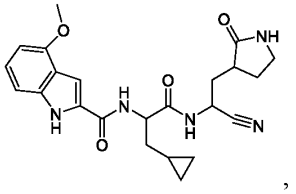
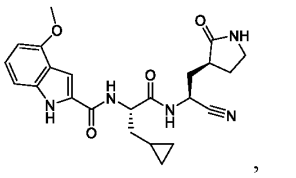
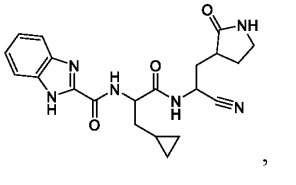

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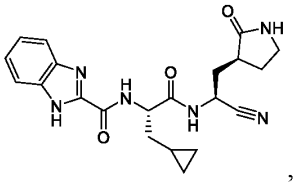
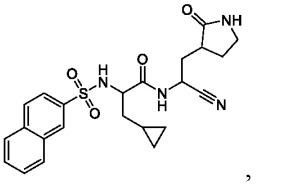
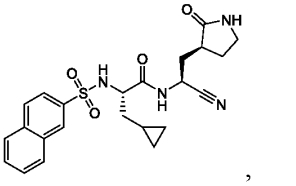
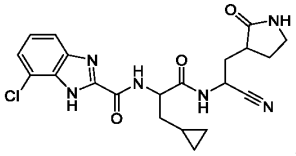
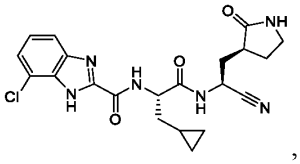
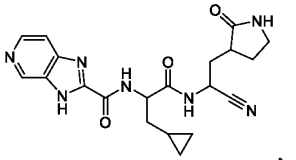
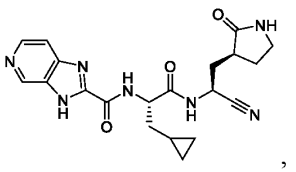
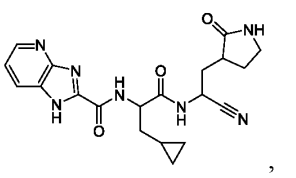
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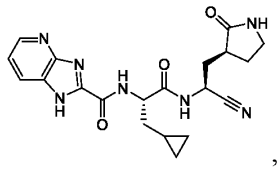
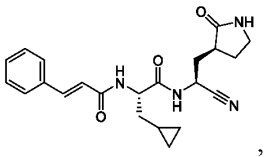
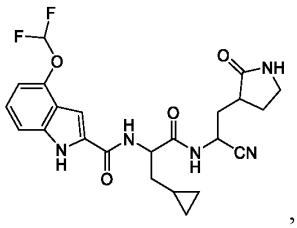
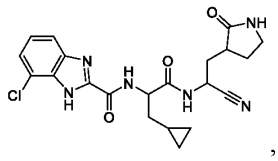
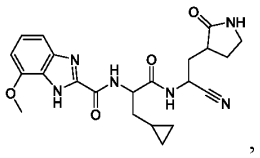
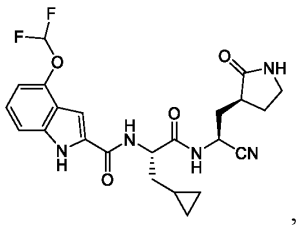
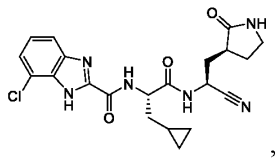
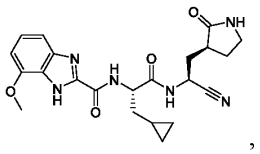
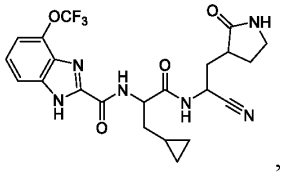
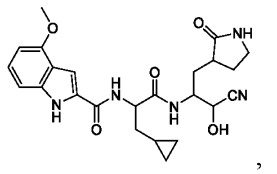
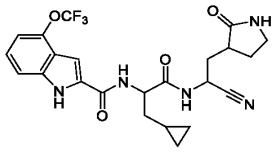
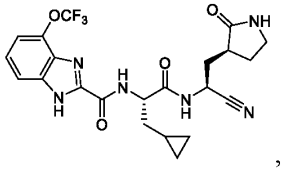
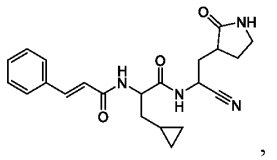
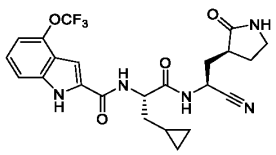
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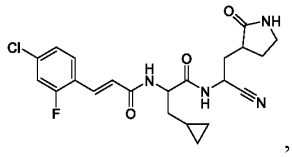
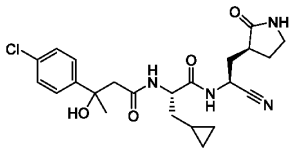
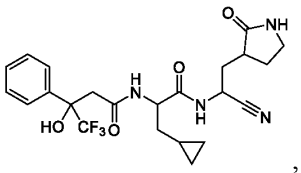
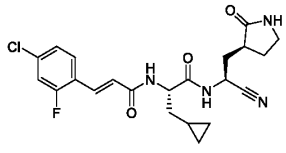
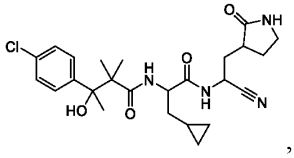
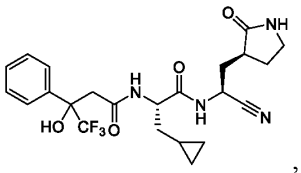
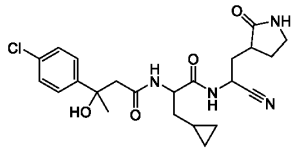
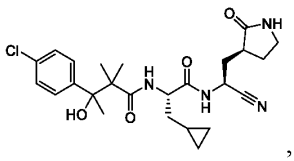
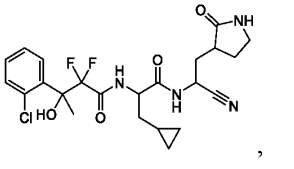
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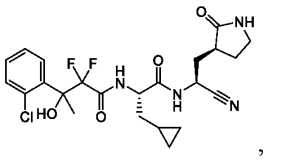

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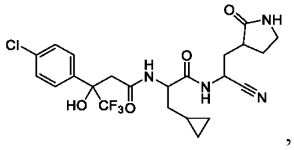
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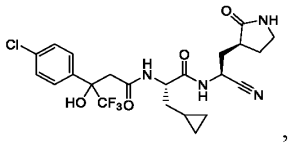
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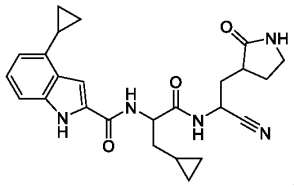
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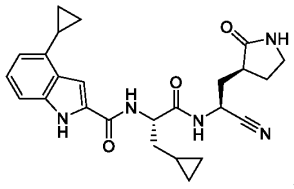
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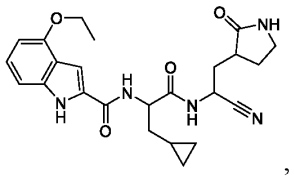
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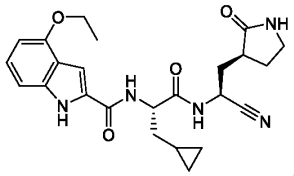
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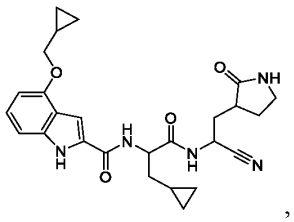
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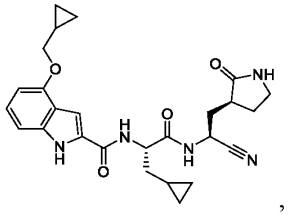
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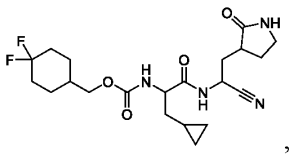
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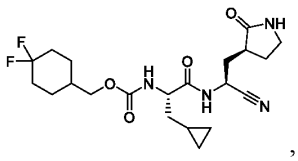
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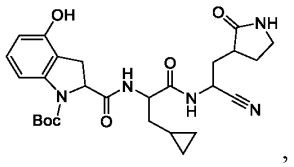
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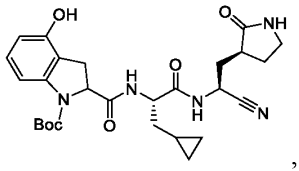
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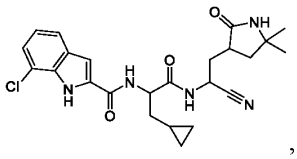
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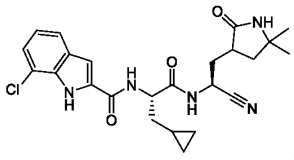
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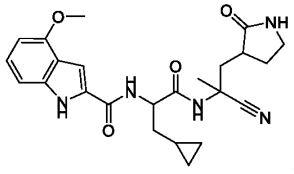
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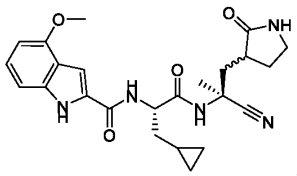
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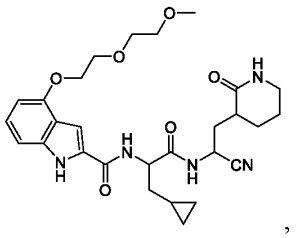
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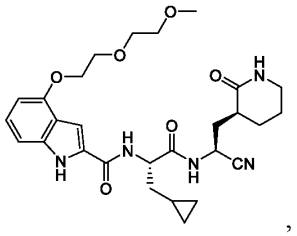
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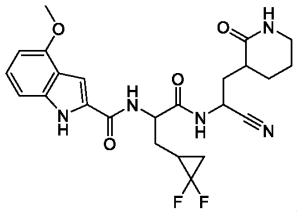
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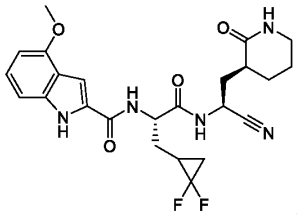
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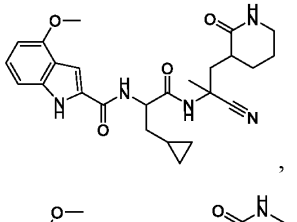
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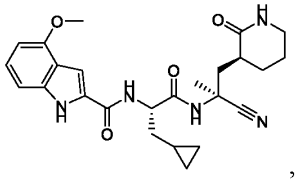


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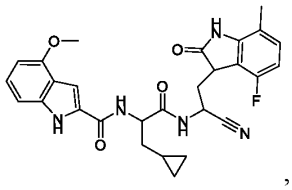
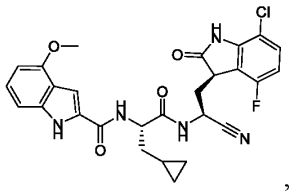
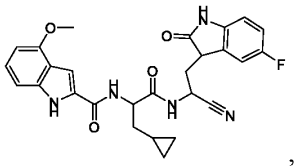
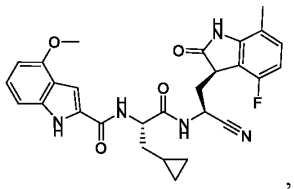
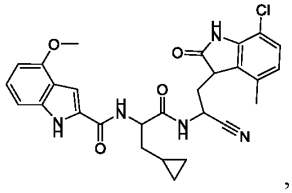
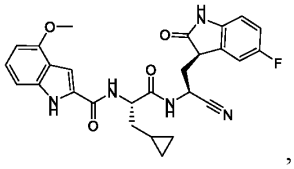
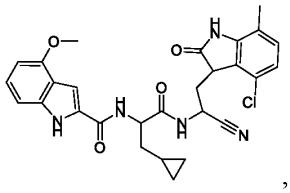
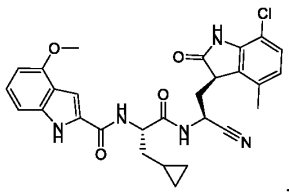
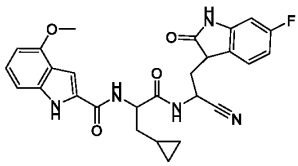
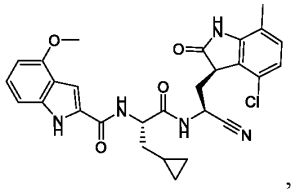
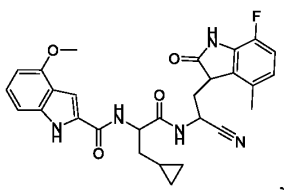
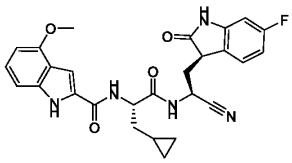
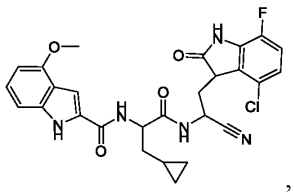
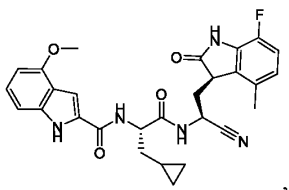
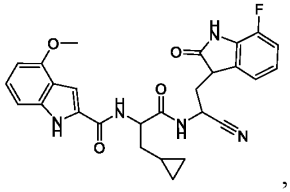
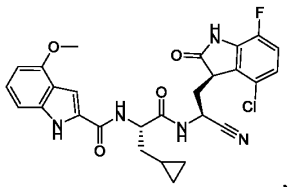
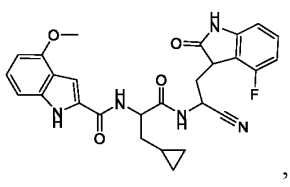
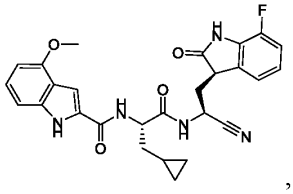
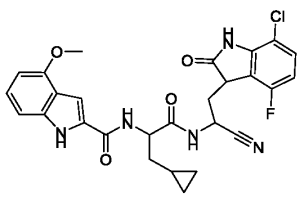
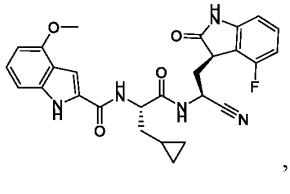
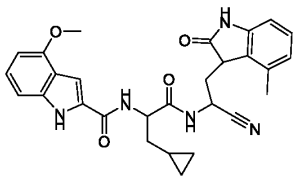


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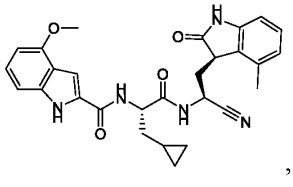
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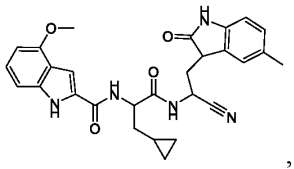
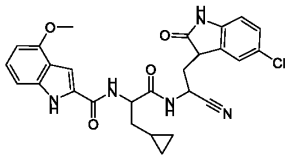
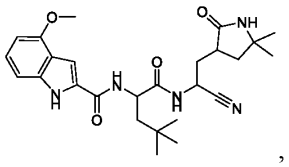
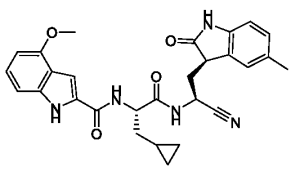
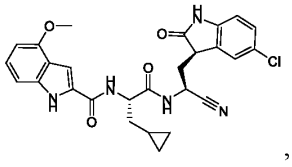
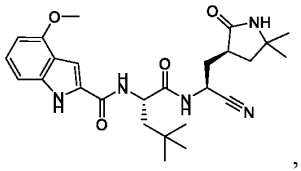
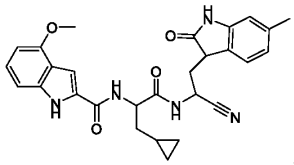
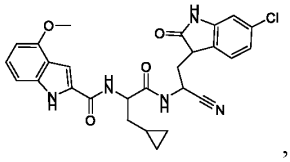
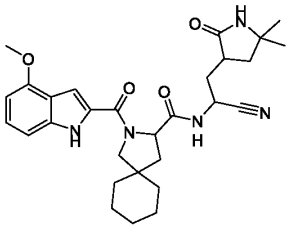
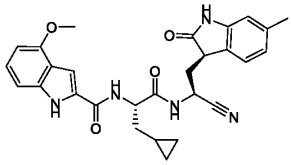
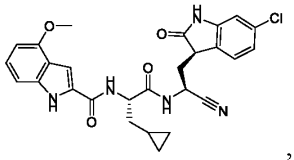
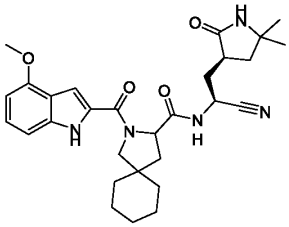
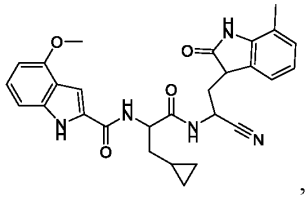
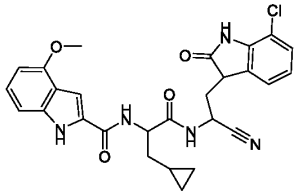
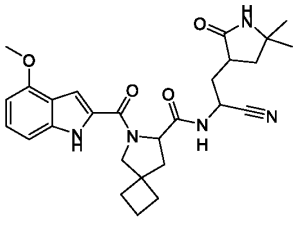
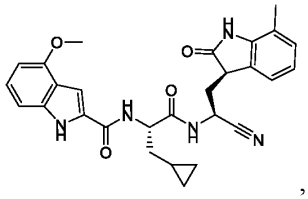
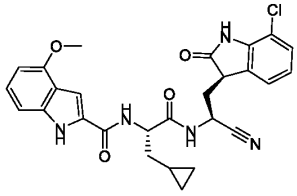


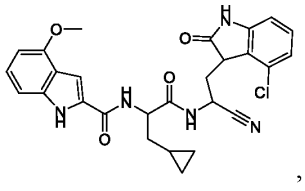
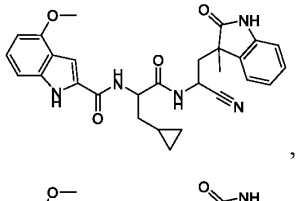
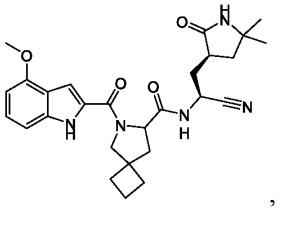
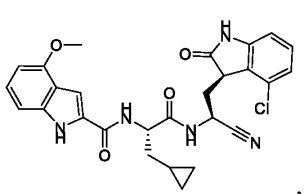
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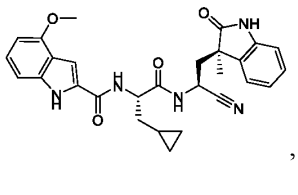
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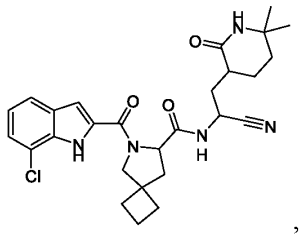
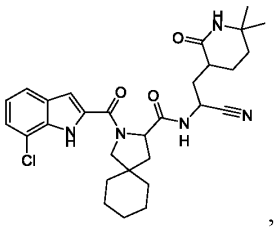
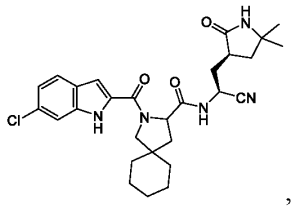
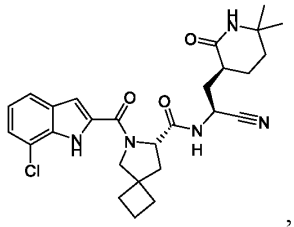
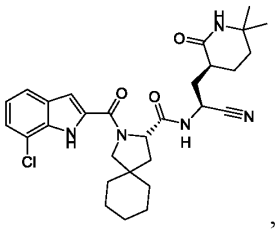
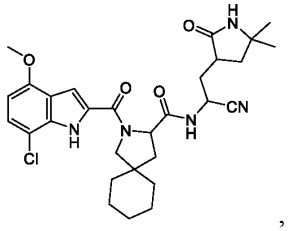
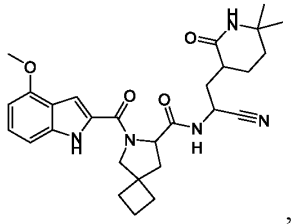
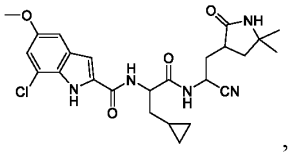
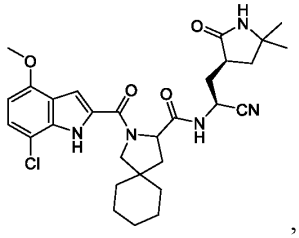
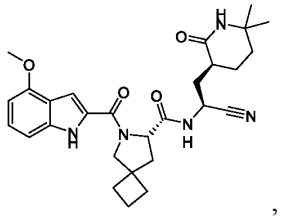
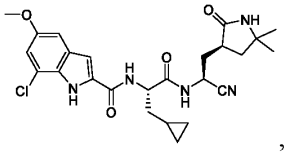
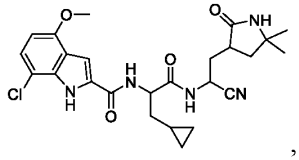
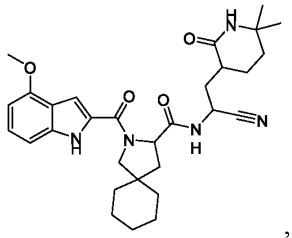
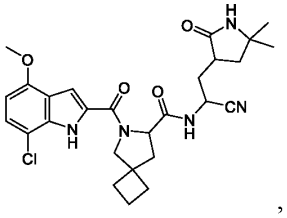
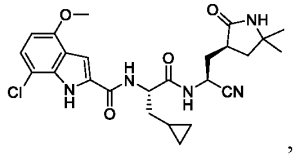
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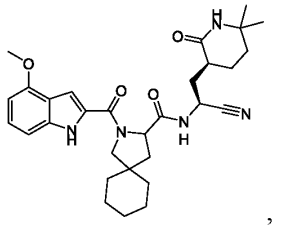
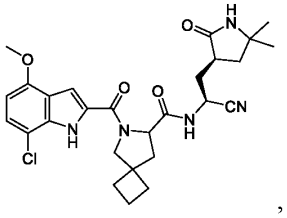
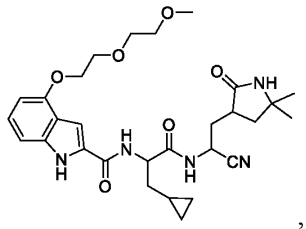
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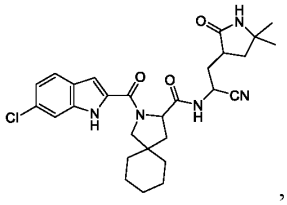
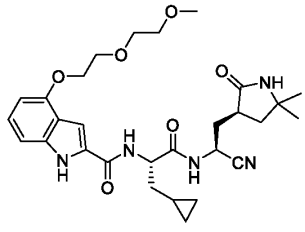
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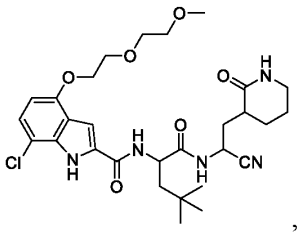
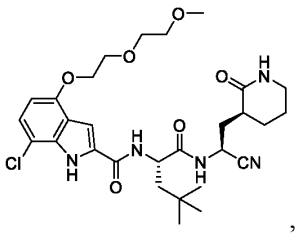
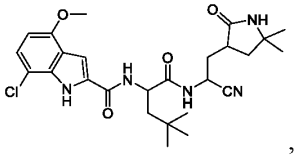
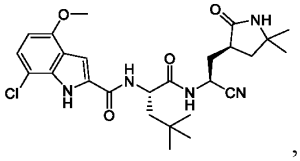
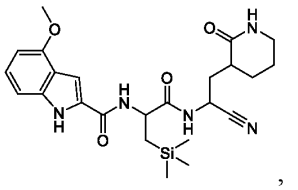
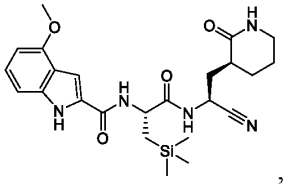
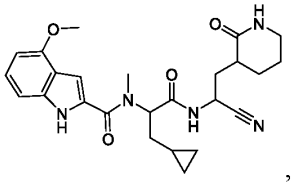
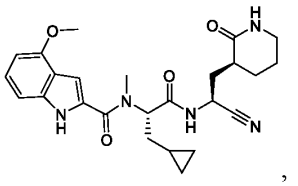
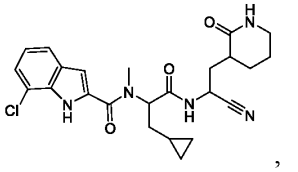
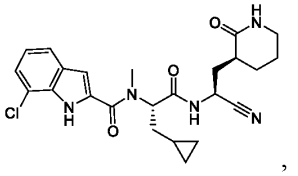
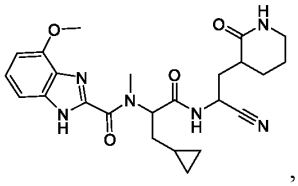
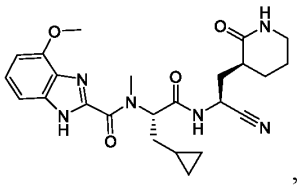
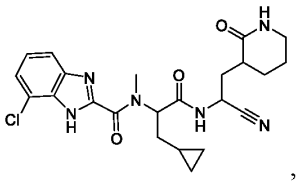
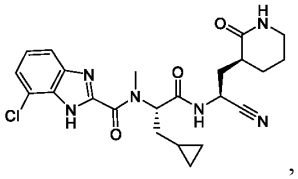
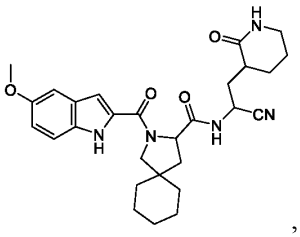
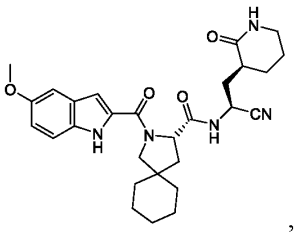
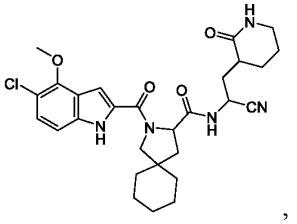
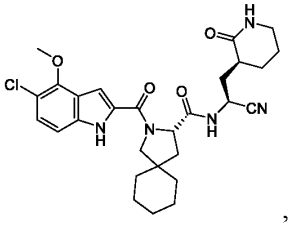
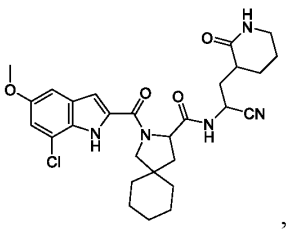
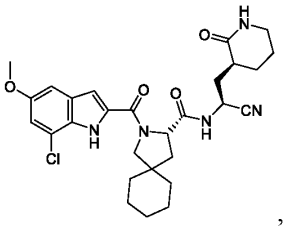

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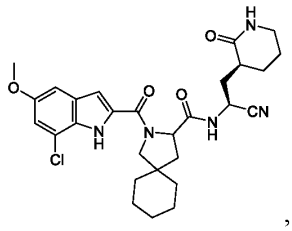
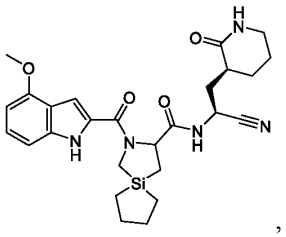
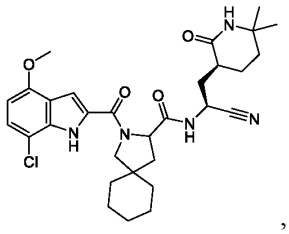
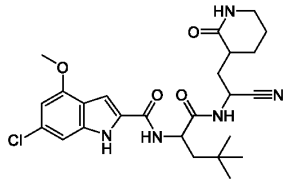
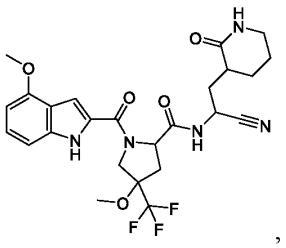
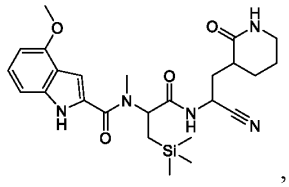
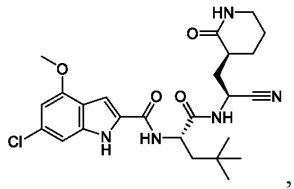
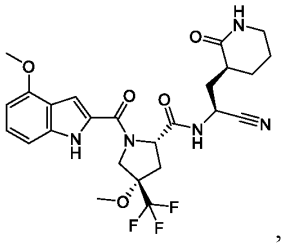
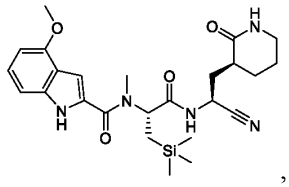
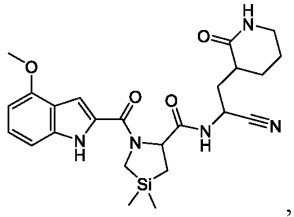
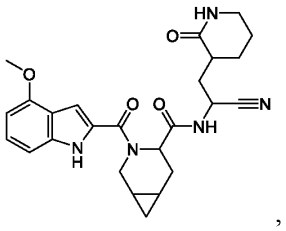
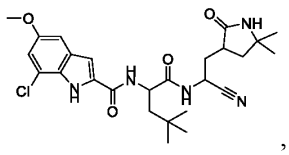
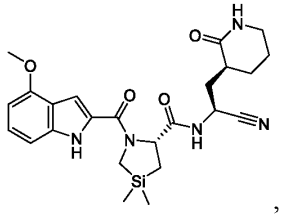
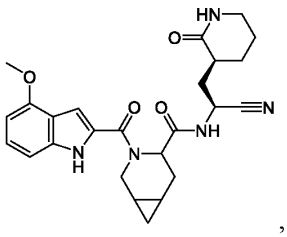
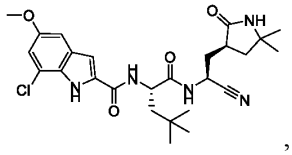
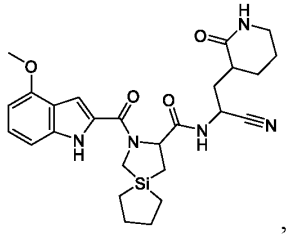
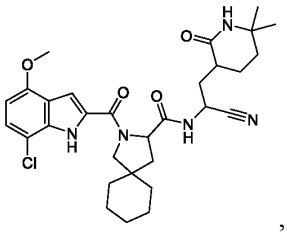
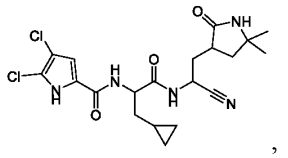
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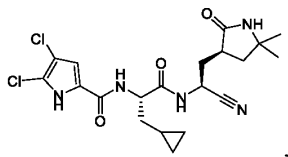
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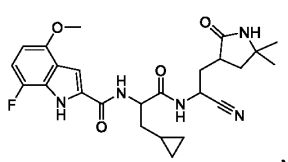
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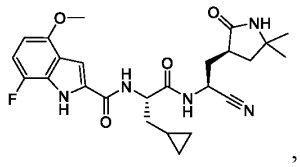
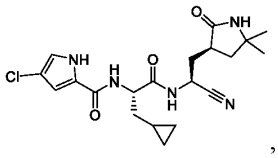
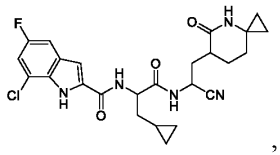
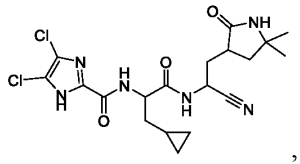
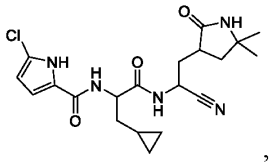
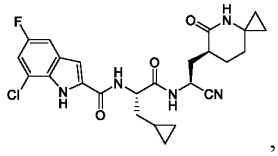
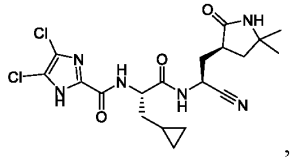
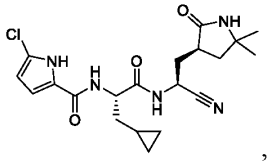
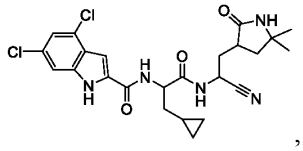
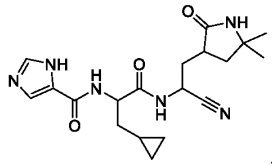
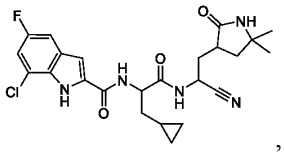
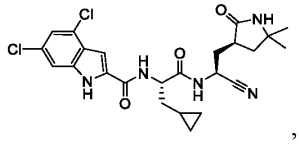
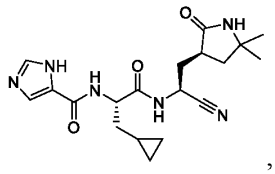
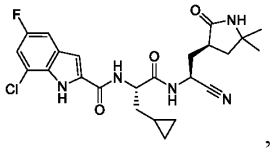
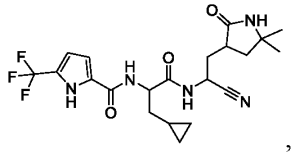
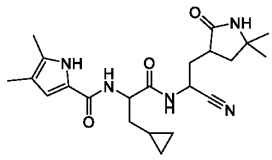
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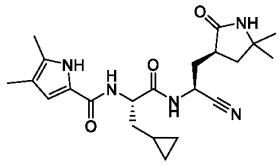
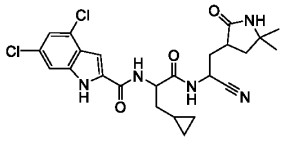
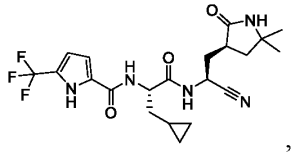
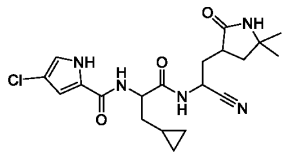
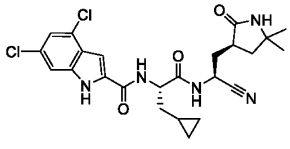
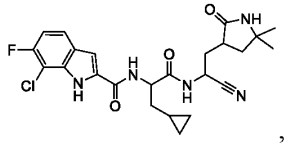
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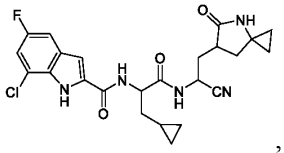
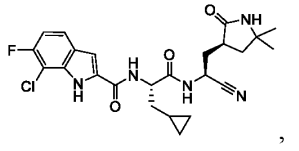
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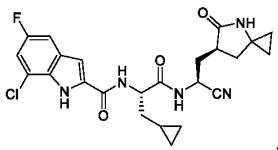
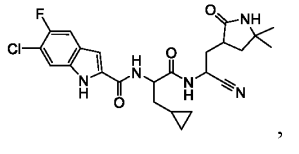
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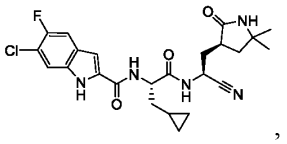
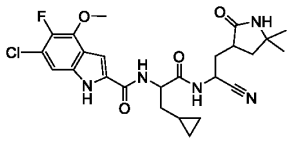
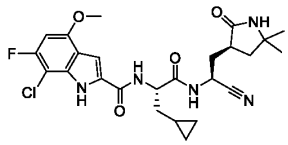
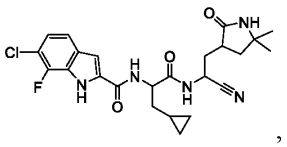
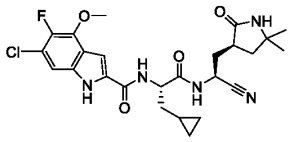
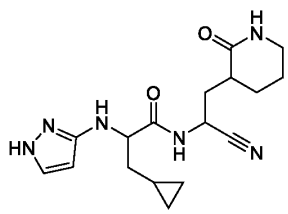
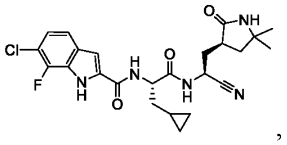
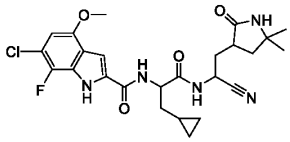
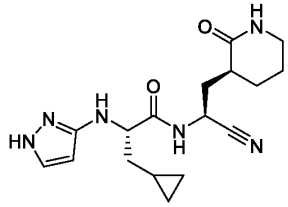
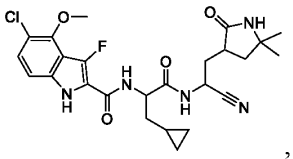
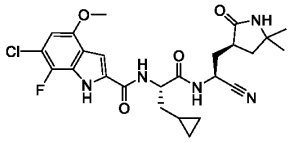
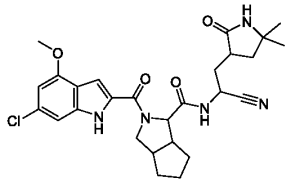
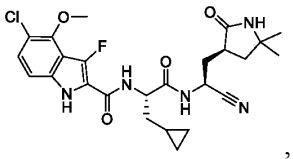
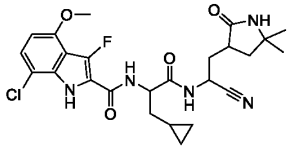
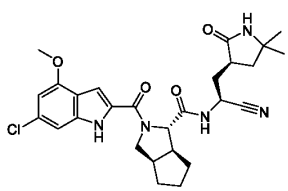
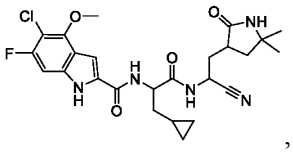
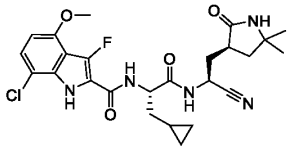
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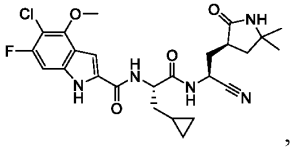
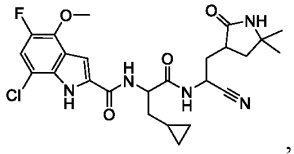
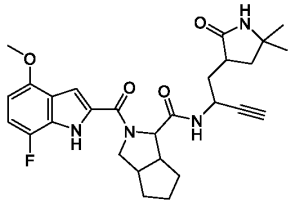
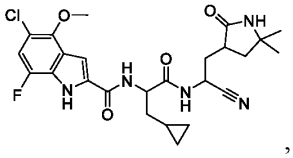
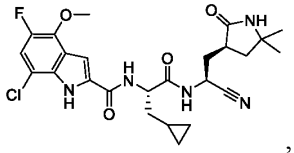
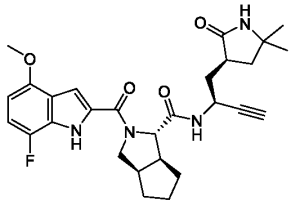
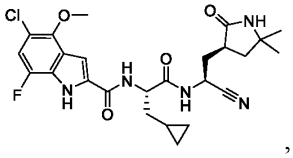
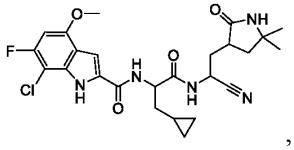
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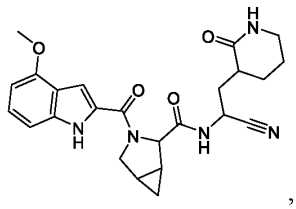
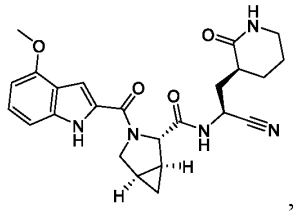
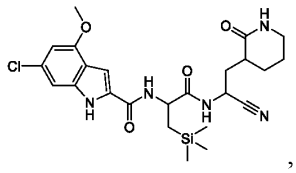
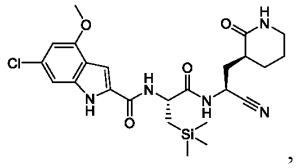
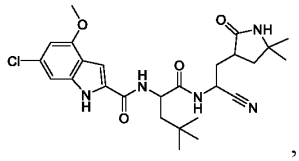
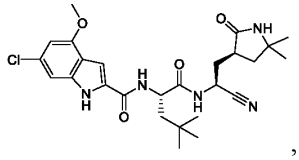
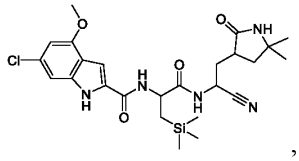
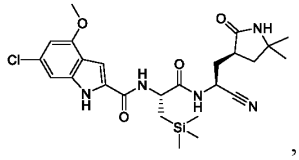
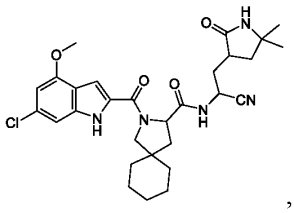
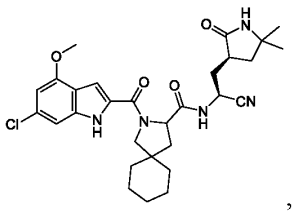
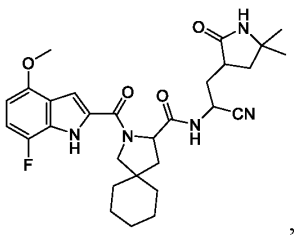
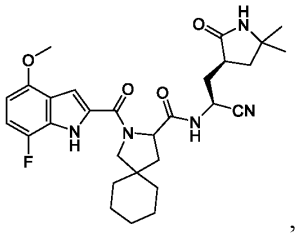
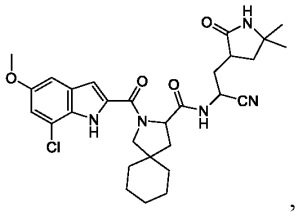
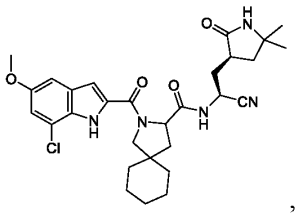
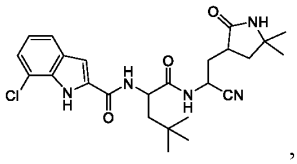
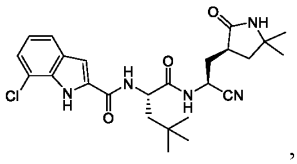
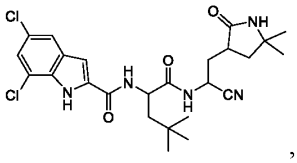
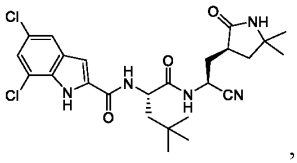
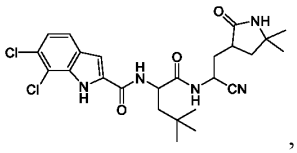
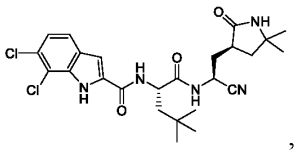
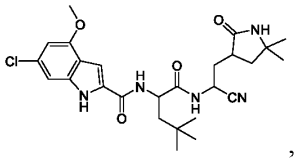
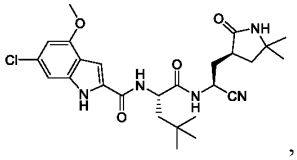
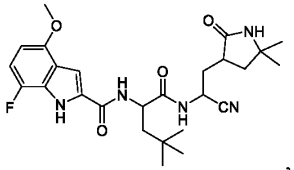
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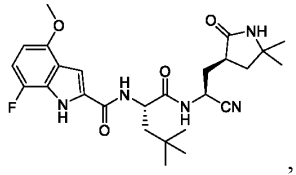
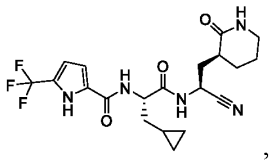
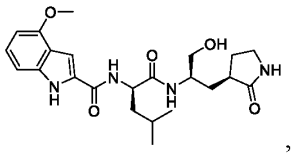
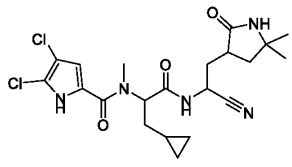
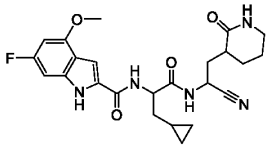
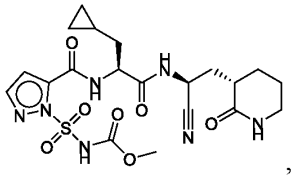
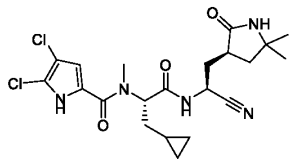
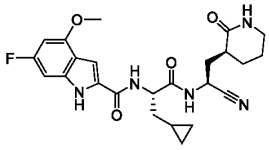
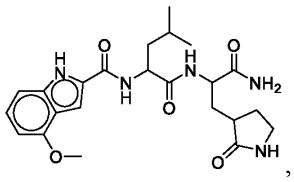
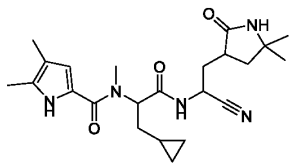
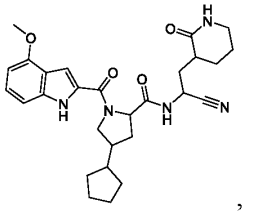
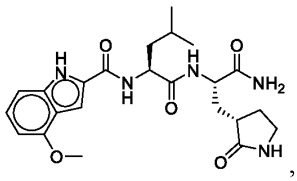
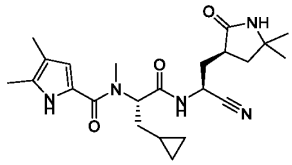
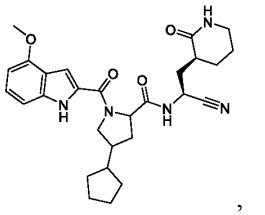
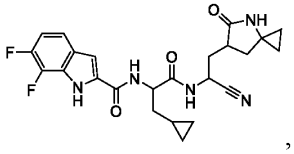
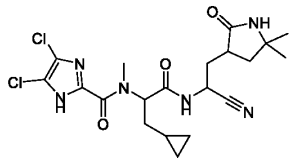
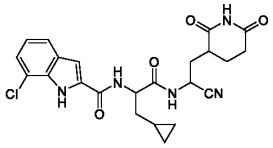
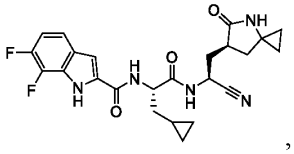
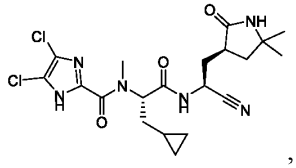
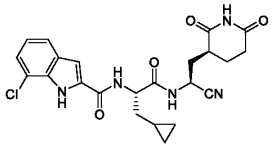
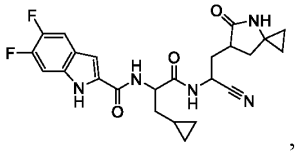
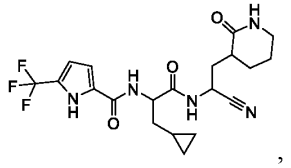
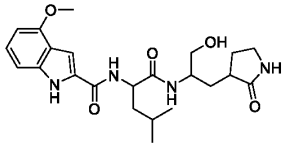
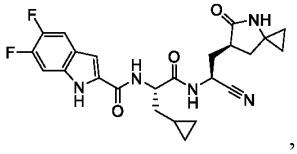
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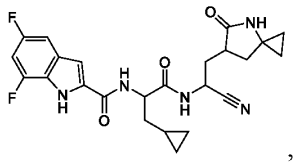
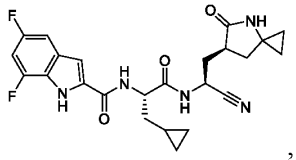
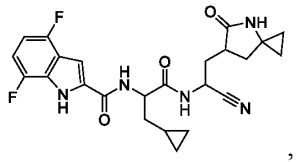
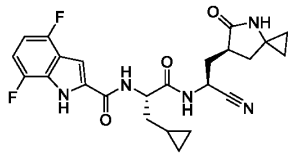
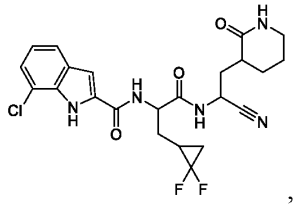
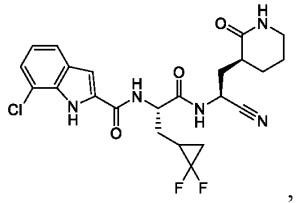
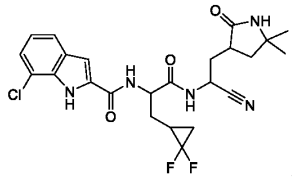
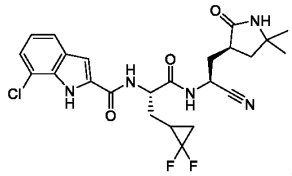
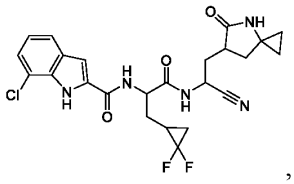
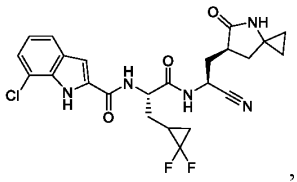
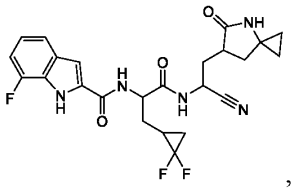
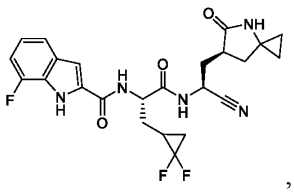
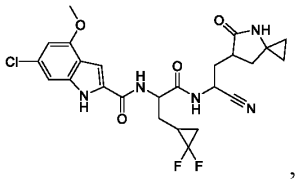
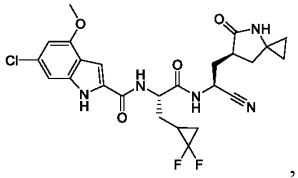
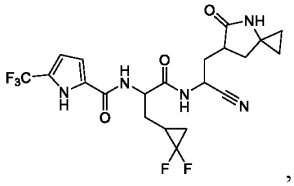
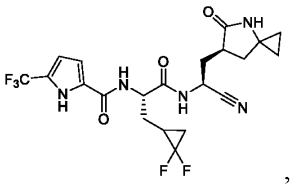
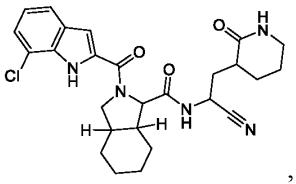
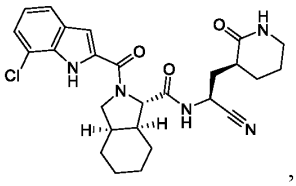
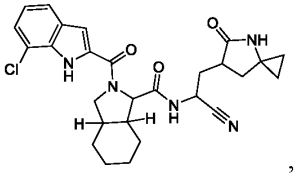
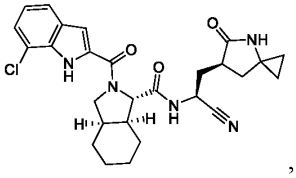
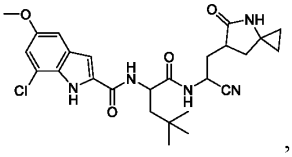
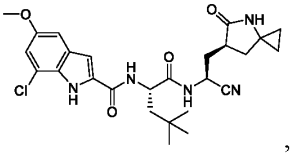
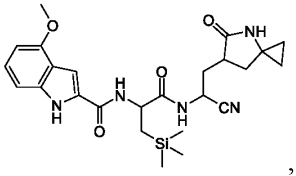
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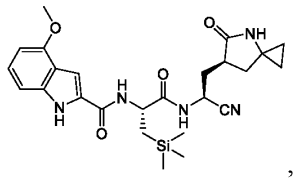
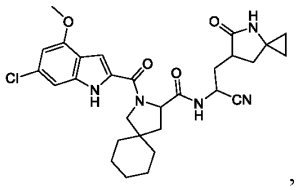
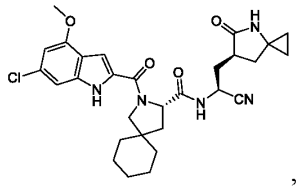
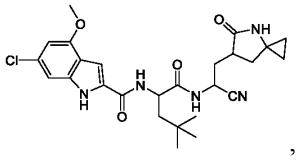
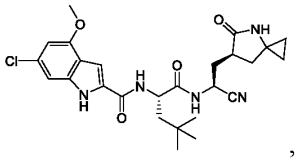
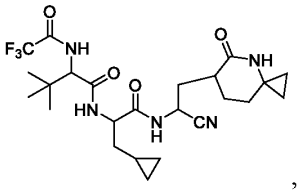
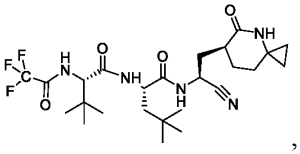
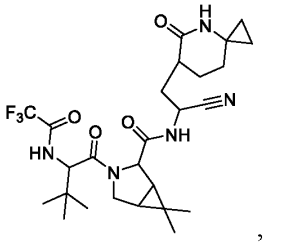
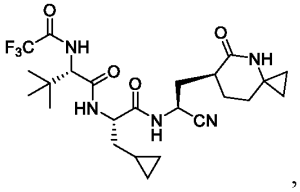
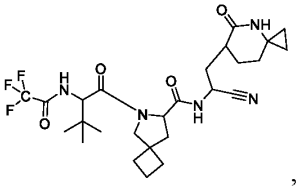
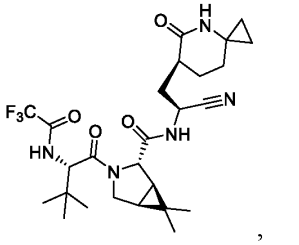
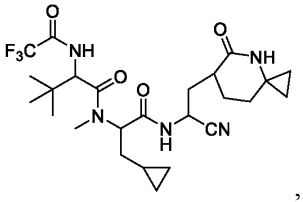
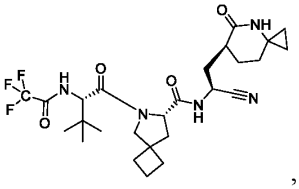
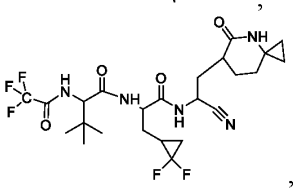
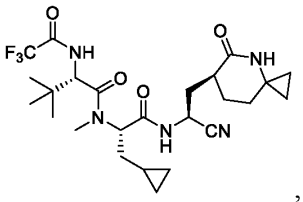
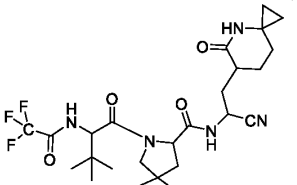
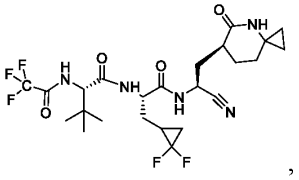
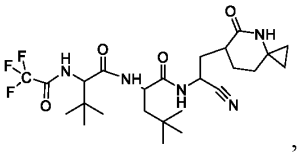
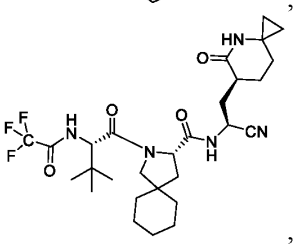
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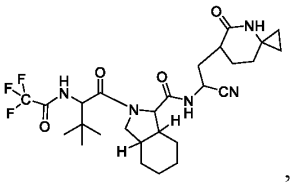
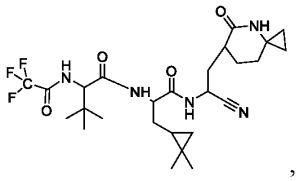
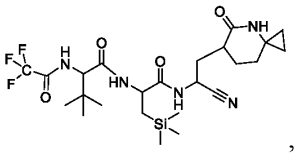
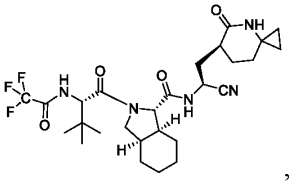
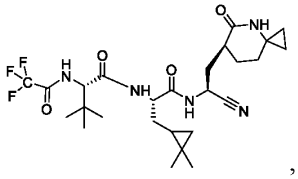
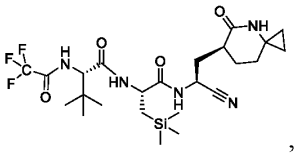
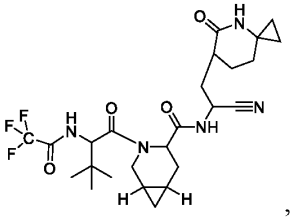
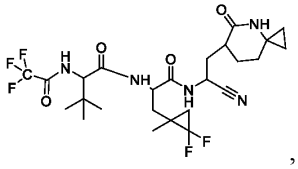
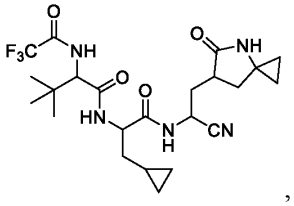
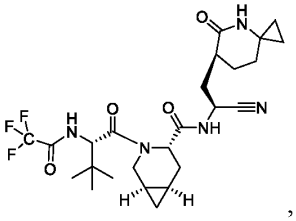
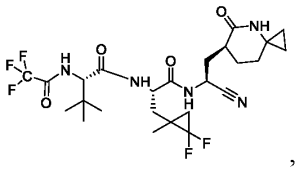
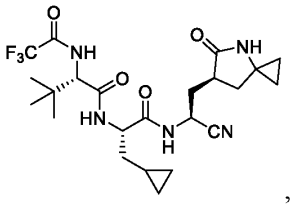
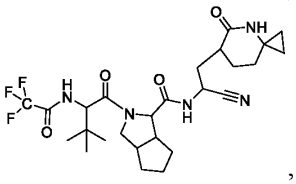
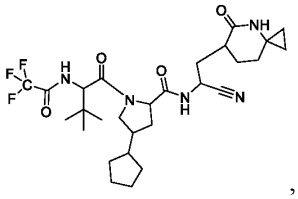
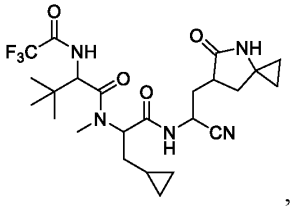
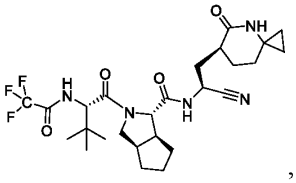
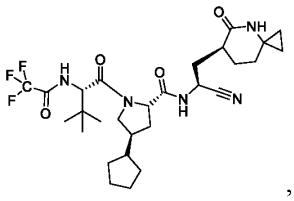
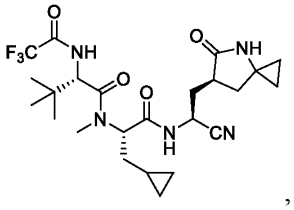
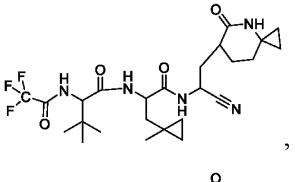
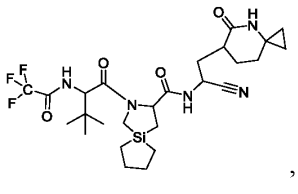
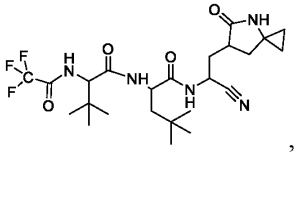
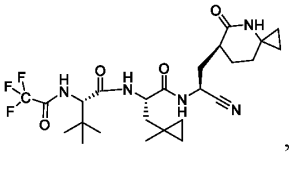
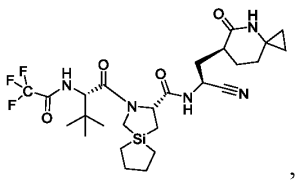
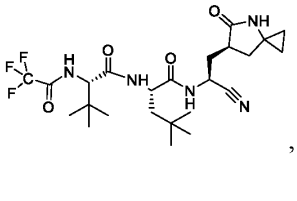
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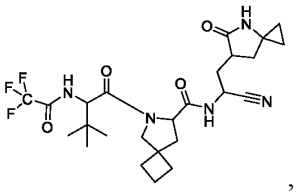
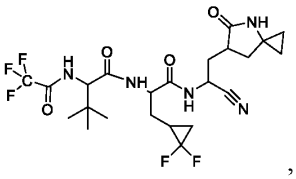
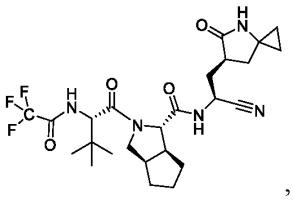
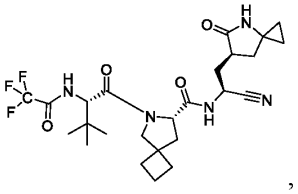
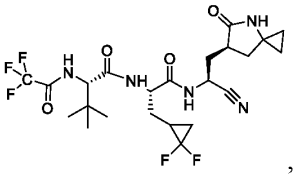
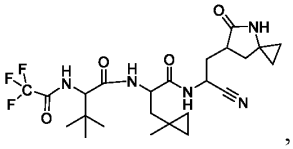
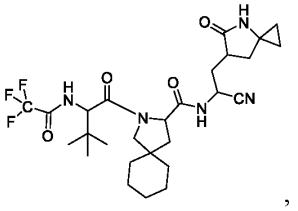
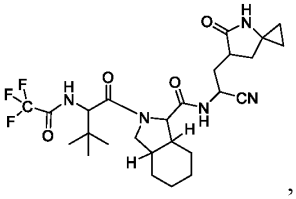
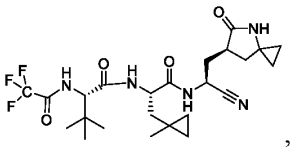
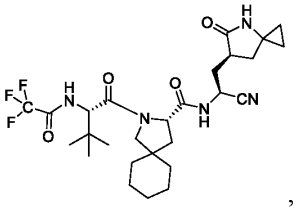
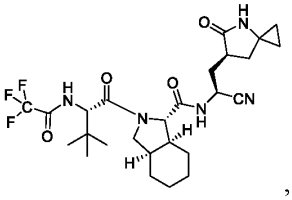
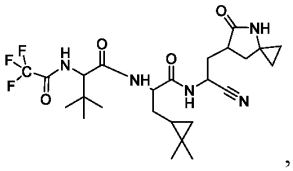
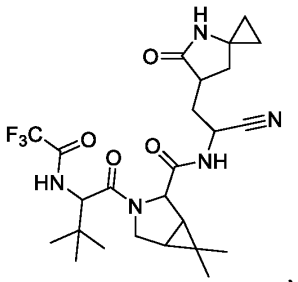
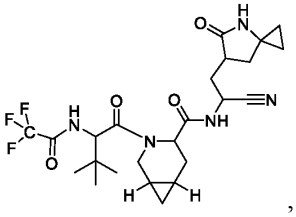
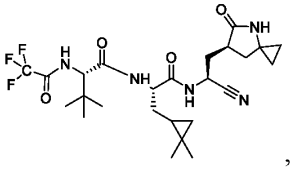
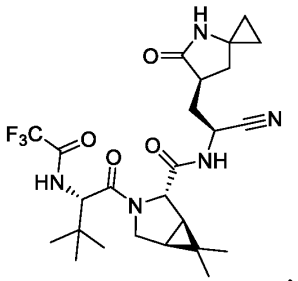
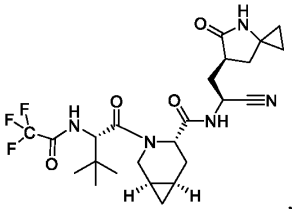
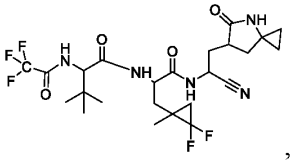
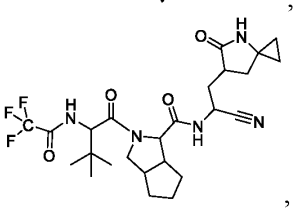
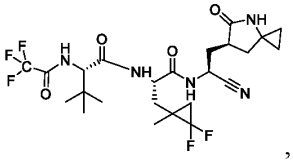

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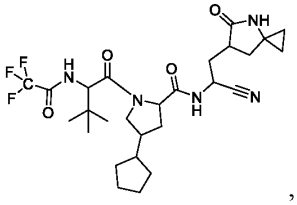

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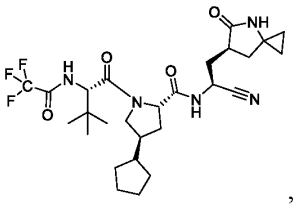
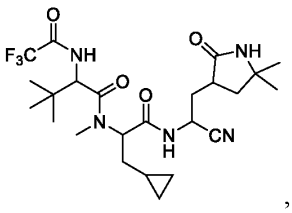
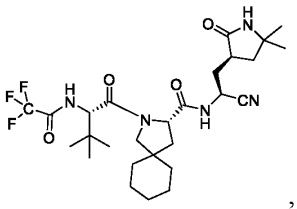
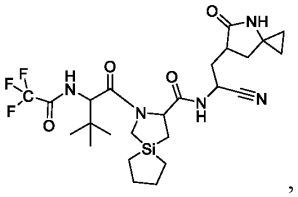
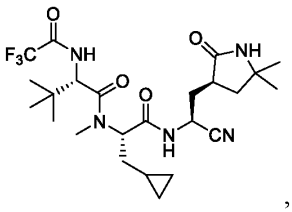
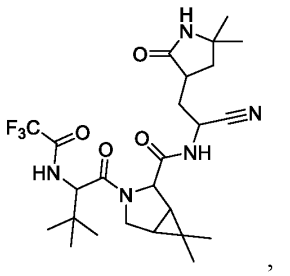
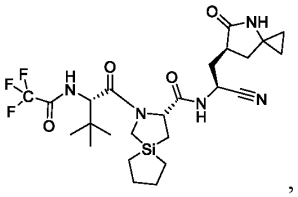
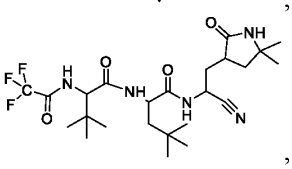
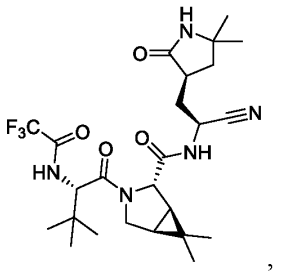
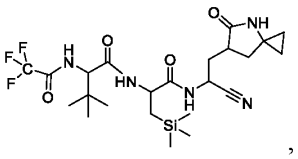
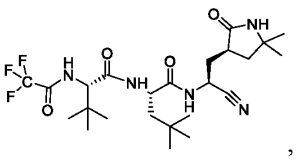
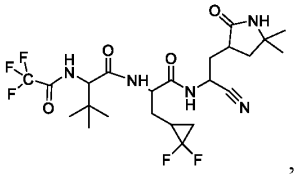
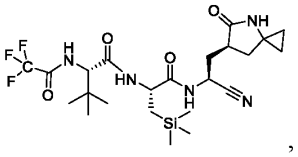
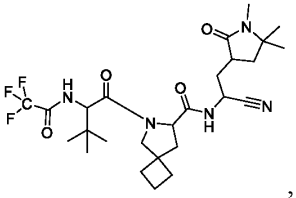
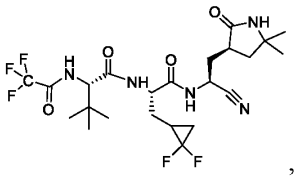
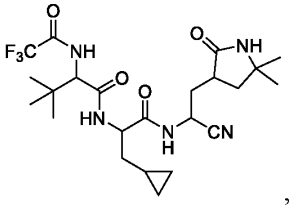
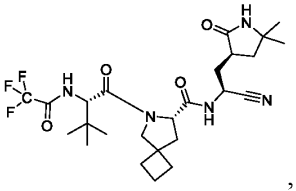
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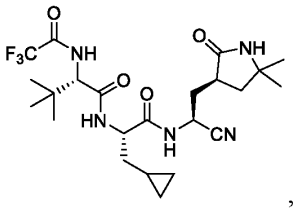
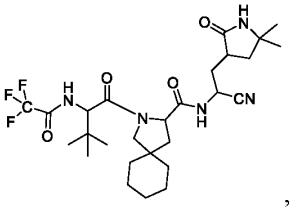
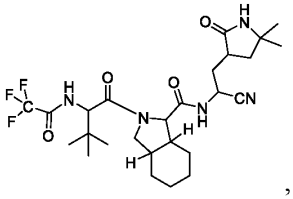
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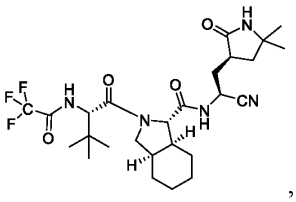
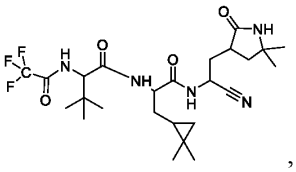
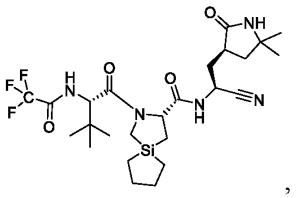
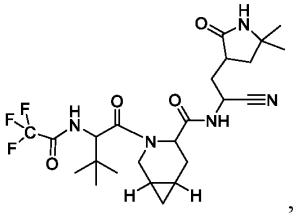
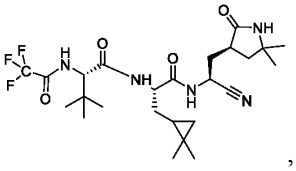
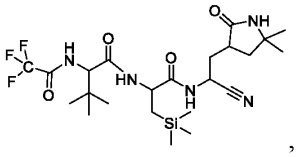
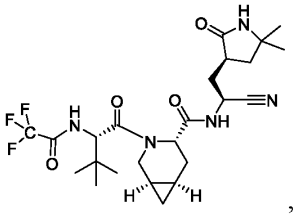
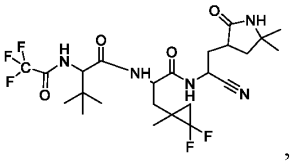
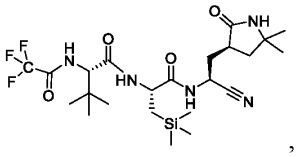
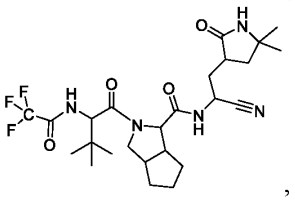
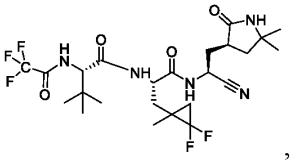
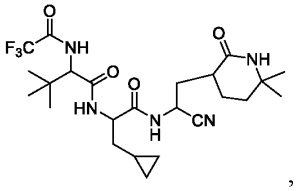
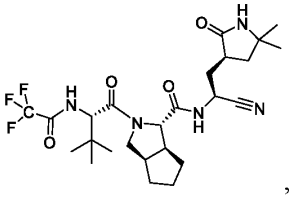
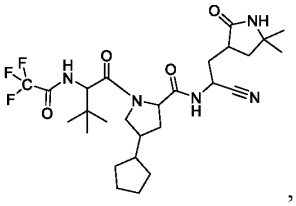
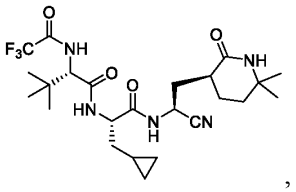
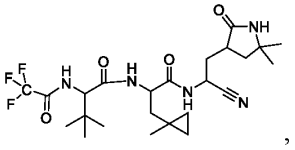
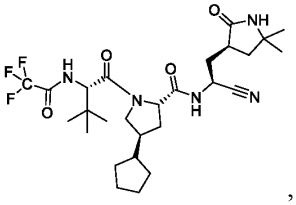
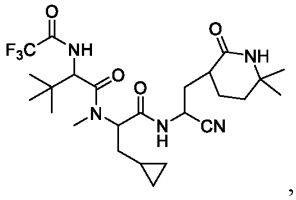
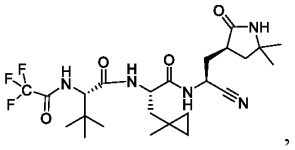
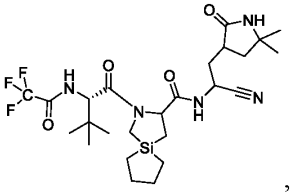
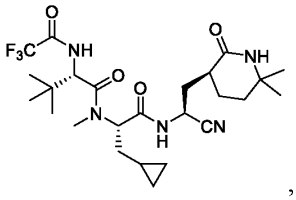
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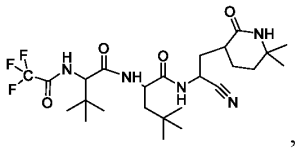
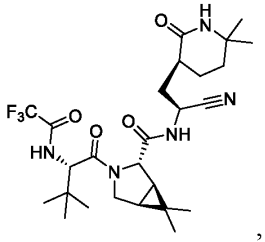
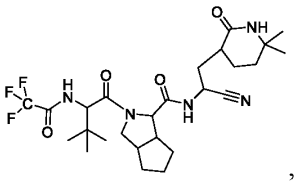
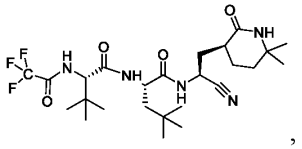
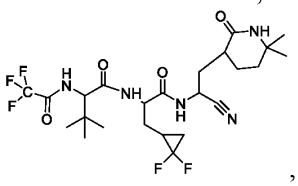
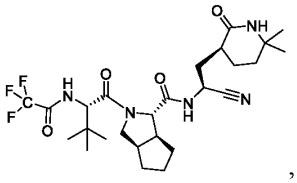
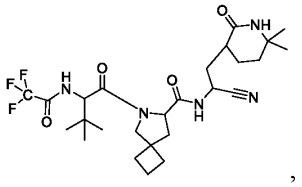
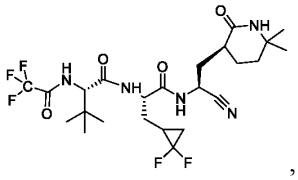
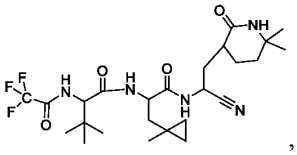
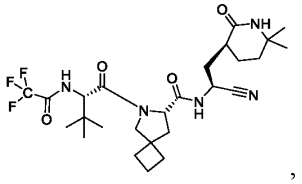
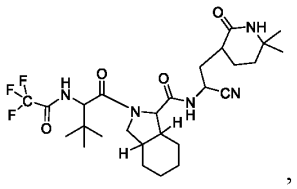
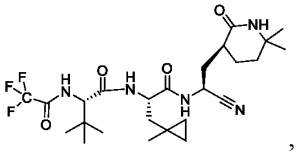
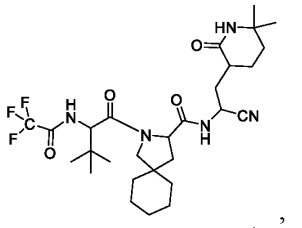
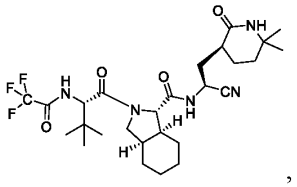
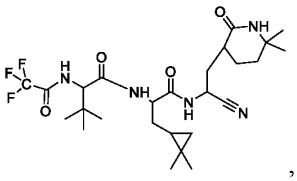
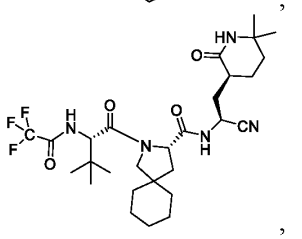
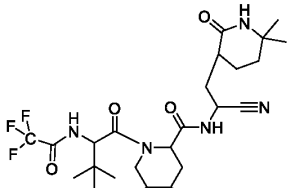
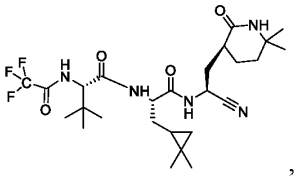
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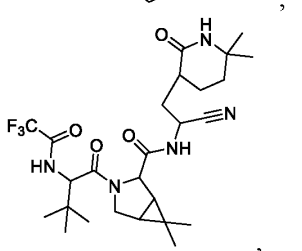
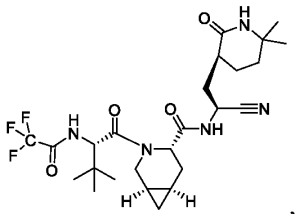
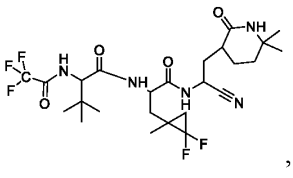
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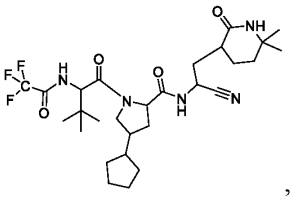
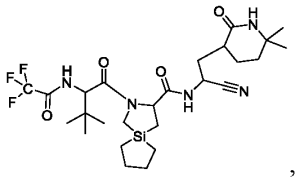
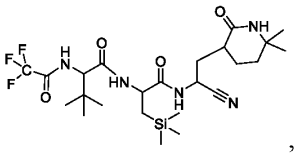
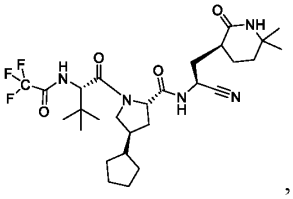
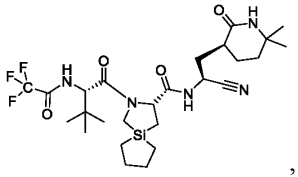
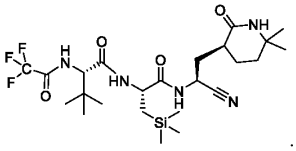
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27. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of any of the compounds of the embodiment.

28. The viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
29. The viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.
30. The viral infection is a coronavirus infection.
31. The viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).
32. The viral infection is SARS-CoV-2.

33. The viral infection is an arenavirus infection.
34. The arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.
35. The viral infection is an influenza infection.
36. The influenza is influenza H1N1, H3N2 or H5N1.
37. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of any compound of the embodiment to a patient suffering from the virus, and/or contacting an effective amount of any compound of the embodiment with a virally infected cell.
38. The further comprises administering another therapeutic.
39. The method further comprises administering an additional anti-viral therapeutic.
40. The anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR-576, and zalcitabine.
41. The another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin,

ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

42. The additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.

43. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of a compound of the embodiment
44. The compound is administered before viral exposure.
45. The compound is administered after viral exposure.

EXAMPLES

[000199] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed.

Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

[000200] At least some of the compounds identified as "Intermediates" herein are contemplated as compounds of the disclosure.

[000201] ^{1}H NMR spectra are recorded at ambient temperature using e.g., a Varian Unity Inova (400 MHz) spectrometer with a triple resonance 5mm probe for Example compounds, and either a Bruker Avance DRX (400 MHz) spectrometer or a Bruker Avance DPX (300 MHz) spectrometer for Intermediate compounds. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br = broad signal, s = singlet, d = doublet, dd = double doublet, dt = double triplet, ddd = double doublet, t = triplet, td = triple doublet, tdd = triple double doublet, q = quartet, m = multiplet.

[000202] Abbreviations:

AcOH	acetic acid
Boc	*tert*- butoxycarbonyl protecting group
CbzCl	benzyl chloroformate
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIEA	N,N-diisopropylethylamine
DIPEA	N,N-diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
EA	ethyl acetate
EtOAc	ethyl acetate
EDCI	1-ethyl-3- (3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid

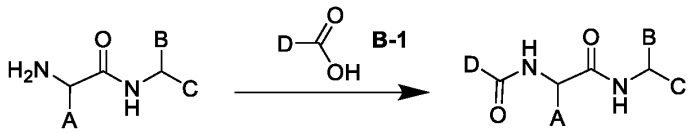
EtOH	ethanol
FA	formic acid
HATU	(1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HOBt	hydroxybenzotirazole
LiHMDS	lithium bis(trimethylsilyl)amide
MTBA	1-4-(3-Methyltriazeno)benzoic acid
MTBE	methyl *tert*-butyl ether
MeOH	methanol
MeCN	acetonitrile
MS	mass spectrometry
NMR	nuclear magnetic resonance
PE	petroleum ether
PMA	phosphomolybdic acid
PMBCl	p-methoxybenzyl chloride
Pht	phthaloyl
PyBOP	(benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate)
t-BuLi	*tert*-butylithium
T_3P	propanephosphonic acid anhydride
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMSCN	trimethylsilyl cyanide

General Chemistry

[000203] Exemplary compounds described herein are available by the general synthetic method illustrated in Scheme 1, including preparations of Intermediates and preparation of accompanying Examples.

Synthetic Scheme(s)

Scheme 1

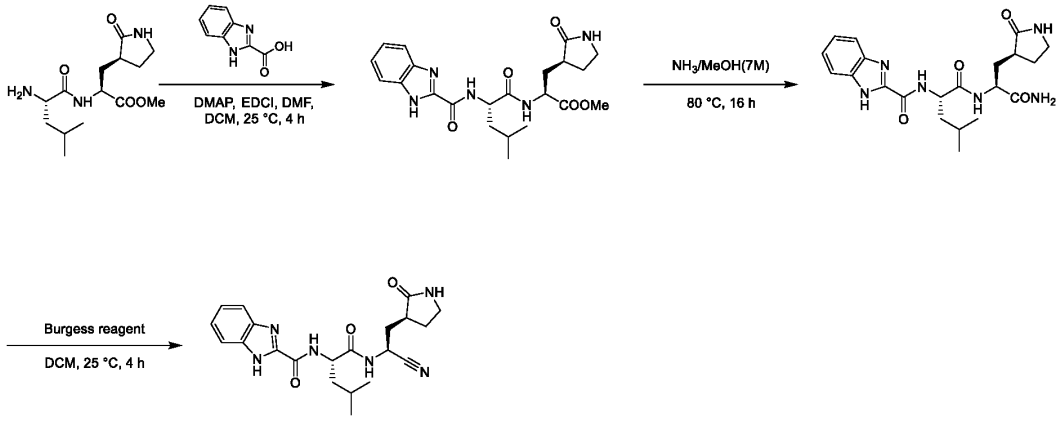


[000204] Scheme 1 illustrates an exemplary preparation of **C-1**. Reacting a solution of amine **A-1**, and acid **B-1** with a coupling agent such as T_3P, EDCI/HOBt, in the presence of a base such as TEA, DMAP and DIEA, and solvent such as DMF and DCM, affords **C-1**.

[000205] In Scheme 1, examples of A include a substituted or unsubstituted alkyl and a substituted or unsubstituted cycloalkyl, examples of B include a warhead moiety, such as cyano, aldehyde, hydroxymethylketone, ketoamide, heteroaryl-ketone, enone, and Michael acceptor warhead, examples of C include an alkyl substituted with a 4-, 5-, or 6-membered lactam, and examples of D include a substituted or unsubstituted bicyclic heteroaryl moiety. In Scheme 1, exemplary preparation of a cyano moiety at B include a dehydration of an amide to nitrile with a dehydration agent such as Burgess reagent.

[000206] Compounds of Table 1 and Table 2 have been prepared following general Scheme 1, which follows the examples described below, such as examples 19, 25, 27, 32, 39, and 41.

Example 1. Synthesis of viral protease inhibitor compound 103



Step 1: (2S)-2-[[(2S)-2-(1H-benzimidazole-2-carbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000207] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 483.81 umol, 1 *eq*, TFA) and 1H-benzimidazole-2-carboxylic acid (94.14 mg, 580.57 umol, 1.2 *eq*) in DCM (2 mL) was added EDCI (185.49 mg, 967.61 umol, 2 *eq*) and DMAP (118.21 mg, 967.61 umol, 2 *eq*). The mixture was added DMF (1 mL) and stirred at 25 °C for 4 h. The resulting mixture was diluted with H_2O (20 mL) and extracted with DCM (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM/MeOH=5/1), to give methyl (2S)-2-[[(2S)-2-(1H-benzimidazole-2-carbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 338.22 umol) as a solid.

Step 2: N-[(1S)-3-methyl-1-[[(1S)-1-(nitrosomethyl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]butyl]-1H-benzimidazole-2-carboxamide

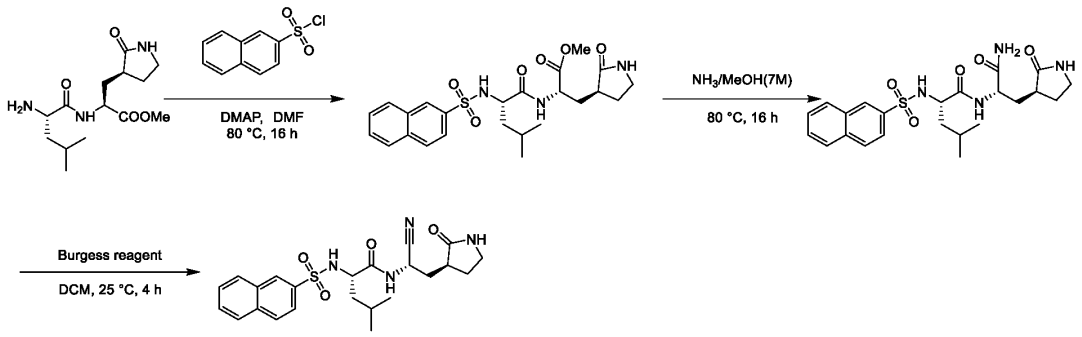
[000208] Methyl(2S)-2-[[(2S)-2-(1H-benzimidazole-2-carbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 338.22 umol, 1 *eq*) was added NH_3/MeOH (7 M, 5 mL, 103.48 *eq*). The mixture was stirred at 80 °C for 16 h in a sealed tube. The reaction was concentrated in vacuo to dryness, give compound N-[(1S)-3-methyl-1-[[(1S)-1-(nitrosomethyl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]butyl]-1H-benzimidazole-2-carboxamide (140 mg, crude) as a solid. The crude product was used directly in next step.

Step 3: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-1H-benzimidazole-2-carboxamide

[000209] N-[(1S)-3-methyl-1-[[(1S)-1-(nitrosomethyl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]butyl]-1H-benzimidazole-2-carboxamide (120.00 mg, 280.06 umol, 1 *eq*) in DCM (5 mL) was added Burgess reagent (150 mg, 629.45 umol, 2.25 *eq*). The mixture was stirred at 25 °C for 4 h. The reaction was blow-dried under N_2. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(10 mM NH4HCO3)-ACN];B%: 20%-40%,8 min), give N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-

1H-benzimidazole-2-carboxamide (40 mg, 97.45 umol) was obtained as a solid. MS (ESI) *m/z* 411.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 13.11 (br s, 1H), 8.97 - 8.81 (m, 2H), 7.90 - 7.64 (m, 2H), 7.54 (br s, 1H), 7.31 (br s, 2H), 5.08 - 4.93 (m, 1H), 4.62 - 4.43 (m, 1H), 3.19 - 3.05 (m, 2H), 2.44 - 2.29 (m, 1H), 2.23 - 2.05 (m, 2H), 1.91 - 1.50 (m, 5H), 0.91 (dd, *J*=6.3, 8.9 Hz, 6H).

Example 2. Synthesis of viral protease inhibitor compound 105



Step 1: (2S)-2-[[(2S)-4-methyl-2-(2-naphthylsulfonylamino)pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000210] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 501.06 umol, 1 *eq*) in DMF (5 mL) was added naphthalene-2-sulfonyl chloride (227.16 mg, 1.00 mmol, 2 *eq*) and DMAP (155.35 mg, 1.27 mmol, 2.54 *eq*) and stirred at 25 °C. Then the reaction was stirred at 80 °C for 16 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM/MeOH=10/1). Give methyl (2S)-2-[[(2S)-4-methyl-2-(2-naphthylsulfonylamino)pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (70 mg, 142.98 umol) as an oil.

Step 2: (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methyl-2-(2-naphthylsulfonylamino)pentanamide

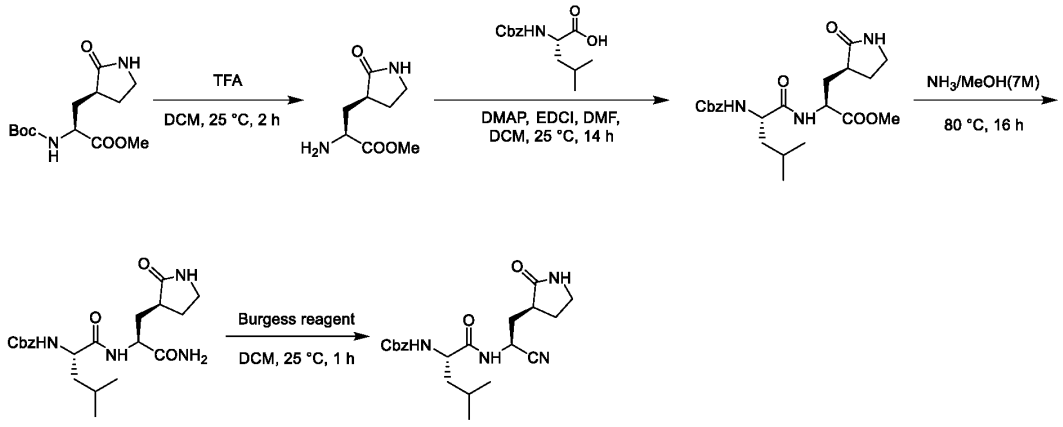
[000211] To a mixture of methyl (2S)-2-[[(2S)-4-methyl-2-(2-naphthylsulfonylamino)pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (50 mg, 102.13 umol, 1 *eq*) was added NH_3/MeOH (7 M, 10 mL, 685.42 *eq*) and stirred at

80 °C for 16 h. The reaction was concentrated in vacuo to dryness to give the crude of (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methyl-2-(2-naphthylsulfonylamino)pentanamide (50 mg, crude) as an oil.

Step 3: (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-2-(2-naphthylsulfonylamino)pentanamide

[000212] (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methyl-2-(2-naphthylsulfonylamino)pentanamide (70 mg, 147.50 umol, 1 *eq*) in DCM (0.5 mL) was added Burgess reagent (79.00 mg, 331.52 umol, 2.25 *eq*). The mixture was stirred at 25 °C for 4 h. The reaction was blow-dried under N_2. The residue was purified by prep-HPLC: column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 25%-55%, 8 min, give compound (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-2-(2-naphthylsulfonylamino)pentanamide (30 mg, 65.71 umol) as a solid. MS (ESI) *m/z* 457.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (br d, *J*=7.5 Hz, 1H), 8.38 (s, 1H), 8.21 (br s, 1H), 8.12 - 8.03 (m, 2H), 8.00 (d, *J*=7.7 Hz, 1H), 7.82 - 7.72 (m, 1H), 7.71 - 7.56 (m, 3H), 4.64 (q, *J*=7.6 Hz, 1H), 3.78 - 3.67 (m, 1H), 3.09 - 3.01 (m, 1H), 3.00 - 2.89 (m, 1H), 2.08 - 1.96 (m, 1H), 1.90 - 1.78 (m, 1H), 1.71 - 1.60 (m, 1H), 1.58 - 1.33 (m, 4H), 1.31 - 1.19 (m, 1H), 0.78 (d, *J*=6.6 Hz, 3H), 0.63 (d, *J*=6.6 Hz, 3H).

Example 3. Synthesis of benzyl N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl] carbamate



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000213] To a mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl] propanoate (300 mg, 1.05 mmol, 1 eq) in DCM (5 mL) was added TFA (4.62 g, 40.52 mmol, 3 mL, 38.67 eq), then the mixture was stirred at 25 °C for 2 h. Once the reaction was completed, the reaction mixture was concentrated under reduced pressure to give a residue and used next step. Compound methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (180 mg, 918.33 umol) was obtained as a colorless oil. MS (ESI) m/z 187.1 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2- oxopyrrolidin-3-yl]propanoate

[000214] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (189.47 mg, 966.66 umol) and (2S)-2-(benzyloxycarbonylamino)-4-methyl-pentanoic acid (256.46 mg, 966.66 umol, 1 *eq*) in DCM (2 mL) was added DMAP (236.19 mg, 1.93 mmol, 2 *eq*) and EDCI (370.62 mg, 1.93 mmol, 2 *eq*). The mixture was added with DMF (1 mL) and stirred at 25 °C for 14 h. Once the reaction was completed, the reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc=3/1 to 0/1) to get the compound methyl (2S)-2-[[(2S)-2-(benzyloxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopy rrolidin-3-yl]propanoate (250 mg, 461.36 umol) as a solid. MS (ESI) *m/z* 434.3 $[M+H]^+$

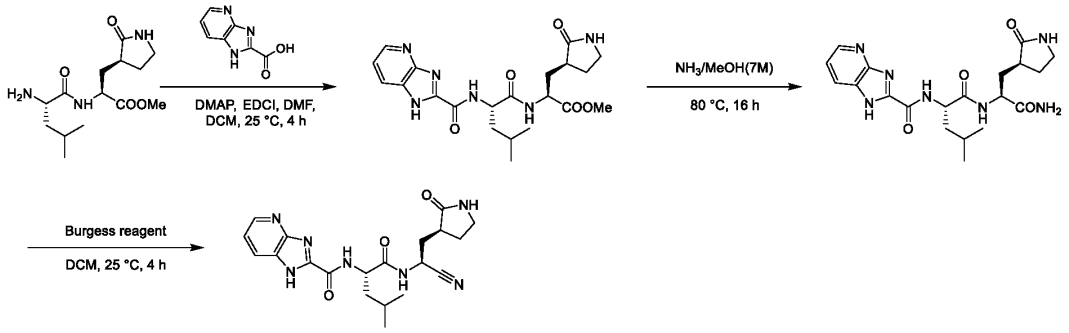
Step 3: benzyl N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoy l]-3-methyl-butyl]carbamate

[000215] Methyl (2S)-2-[[(2S)-2-(benzyloxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 369.09 umol, 1 eq) was added NH_3/MeOH (7 M, 58.14 mL, 1102.58 eq). The mixture was stirred at 80 °C for 16 h. Once the reaction was completed, the reaction mixture was concentrated under reduced pressure to give a residue and used directly next step. Compound benzyl N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl]ethyl]carbamoyl]-3-methyl-butyl]carbamate (150 mg, 322.59 umol) was obtained as a colorless oil.

Step 4: benzyl N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl] carbamate

[000216] To a mixture of benzyl N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamoyl]-3-methyl-butyl]carbamate (150 mg, 179.22 umol, 1 eq) in DCM (5 mL) was added Burgess reagent (42.71 mg, 179.22 umol, 1 eq). The mixture was stirred at 25 °C for 1 h. Once the reaction was completed, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC (column:Waters Xbridge BEH C18 100*30 mm*10 um;mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 20%-50%,8 min) to get the compound benzyl N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]carbamate (28 mg, 69.92 umol) as a solid. MS (ESI) *m/z* 401.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (br d, *J*=7.9 Hz, 1H), 7.70 (s, 1H), 7.54 (br d, *J*=7.8 Hz, 1H), 7.41 - 7.24 (m, 5H), 5.02 (s, 2H), 4.97 - 4.88 (m, 1H), 4.07 - 3.91 (m, 1H), 3.20 - 2.94 (m, 2H), 2.38 - 2.22 (m, 1H), 2.22 - 1.98 (m, 2H), 1.85 - 1.26 (m, 5H), 0.87 (br dd, *J*=6.5, 11.2 Hz, 6H)

Example 4. Synthesis of viral protease inhibitor compound 131



Step 1: (2S)-2-[[(2S)-2-(1H-imidazo[4,5-b]pyridine-2-carbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000217] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 604.76 umol, 1 *eq*, TFA) and 1H-imidazo[4,5-b]pyridine-2-carboxylic acid (118.39 mg, 725.71 umol, 1.2 *eq*) in DCM (4 mL) was added EDCI (231.86 mg, 1.21 mmol, 2 *eq*) and DMAP (147.77 mg, 1.21 mmol, 2 *eq*). The mixture was added with DMF (2 mL) and stirred at 25 °C for 4 h. The reaction

mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM/MeOH=5/1) to give compound methyl (2S)-2-[[(2S)-2-(1H-imidazo[4,5-b]pyridine-2-carbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (100 mg, 224.98 umol) as a solid.

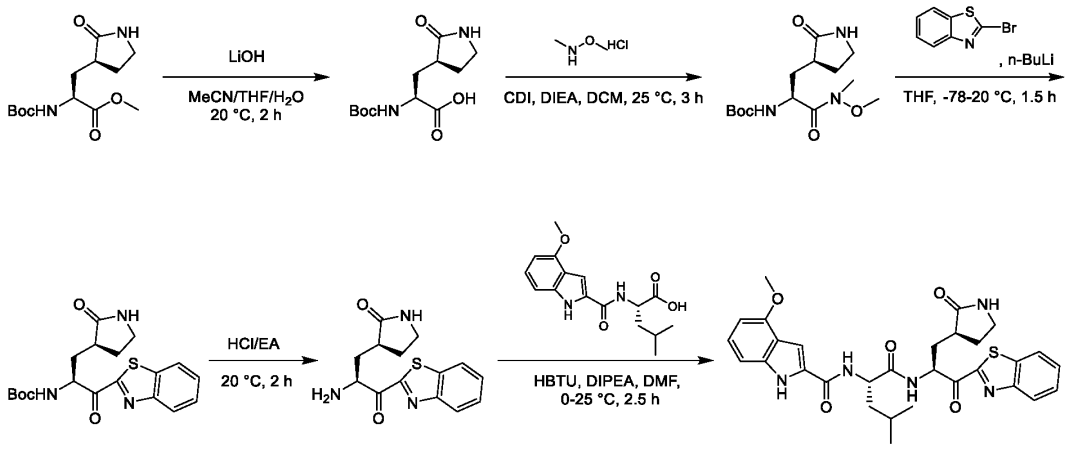
Step 2: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-1H-imidazo[4,5-b]pyridine-2-carboxamide

[000218] To a mixture of methyl (2S)-2-[[(2S)-2-(1H-imidazo[4,5-b]pyridine-2-carbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (100 mg, 224.98 umol, 1 *eq*) was added NH_3/MeOH (7 M, 27.54 mL, 856.77 *eq*) and stirred at 80 °C for 16 h. The reaction was concentrated in vacuo to dryness to give the crude of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-1H-imidazo[4,5-b]pyridine-2-carboxamide (90 mg, crude) as an oil.

Step 3: N-[(1S)-1-[[(1S)-1-cyano-2-[(3 S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-1H-imidazo[4,5-b]pyridine-2-carboxamide

[000219] N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-1H-imidazo[4,5-b]pyridine-2-carboxamide (80 mg, 186.28 umol, 1 *eq*) in DCM (3 mL) was added Burgess reagent (100.00 mg, 419.62 umol, 2.25 *eq*). The mixture was stirred at 25 °C for 4 h. The reaction was blow-dried under N_2. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(10 mM NH4HCO3)-ACN];B%: 10%-35%,8 min) to give N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-1H-imidazo[4,5-b]pyridine-2-carboxamide (25 mg, 60.76 umol) as a solid. MS (ESI) *m/z* 412.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 13.58 (br s, 1H), 9.29 - 8.96 (m, 1H), 8.89 (d, J=7.9 Hz, 1H), 8.49 (br s, 1H), 8.28 - 7.84 (m, 1H), 7.71 (s, 1H), 7.36 (dd, J=4.6, 8.2 Hz, 1H), 5.06 - 4.93 (m, 1H), 4.61 - 4.44 (m, 1H), 3.20 - 3.06 (m, 2H), 2.43 - 2.31 (m, 1H), 2.20 - 2.07 (m, 2H), 1.90 - 1.53 (m, 5H), 0.92 (dd, J=6.4, 9.5 Hz, 6H).

Example 5. Synthesis of viral protease inhibitor compound 121



Step 1: (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoic acid

[000220] To a mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl] propanoate (1.2 g, 3.77 mmol) in THF (3 mL), ACN (3 mL) and H_2O (3 mL) was added LiOH.H_2O (158.29 mg, 3.77 mmol, 1 *eq*). The mixture was stirred at 25 °C for 2 h. Once the reaction was completed, the solution was concentrated to give a residue, and then the residue was adjusted to pH~4 with HCl. The resulting residue was extracted with EtOAc (20 mL* 3) and brine (20 mL), and then concentrated to give a residue compound (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propaneic acid (1 g, 3.31 mmol) was obtained as an oil. MS (ESI) *m/z* 217.1 $[M+H-56]^+$.

Step 2: tert-butyl N-[(1S)-2-[methoxy(methyl)amino]-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl]carbamate

[000221] To a mixture of (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoic acid (1.0 g, 3.31 mmol) in DCM (20 mL) was added CDI (535.94 mg, 3.31 mmol, 1 eq). The mixture was stirred at 0 °C for 30 min, then added with DIEA (512.61 mg, 3.97 mmol, 690.85 uL, 1.2 eq) and N,O-DIMETHYLHYDROXYLAMINE HYDROCHLORIDE (322.40 mg, 3.31 mmol, 1 eq). The resulting mixture was stirred at 25 °C for 3 h. Once the reaction was complete, the reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc=5/1 to 0/1) to get the compound tert-butyl N-[(1S)-2-

[methoxy(methyl)amino]-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamate (0.9 g, 2.57 mmol) which was obtained as an oil. MS (ESI) *m/z* 316.2 $[M+H]^+$

Step 3: tert-butyl N-[(1S)-2-(1,3-benzothiazol-2-yl)-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamate

[000222] To a mixture of 2-bromo-1,3-benzothiazole (458.22 mg, 2.14 mmol, 1.5 eq) in THF (20 mL) was added n-BuLi (2.5 M, 684.92 uL, 1.2 eq) in one portion at -78 °C under N_2. The mixture was stirred at -78 °C for 30 min, and then added with tert-butyl N-[(1S)-2-[methoxy(methyl)amino]-2-oxo-1-[[(3S)-2- oxopyrrolidin-3-yl]methyl]ethyl]carbamate (500 mg, 1.43 mmol) at -78 °C. The resulting mixture was stirred for 1 hour, and then the reaction mixture was quenched by the addition of NH_4Cl (10 mL) at 0 °C, and then stirred for 10 min at 0 °C. The resulting mixture was diluted with water (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by MPLC (SiO_2, petroleum ether/EtOAc~ MeOH=10/1 to 0/1) to get the compound tert-butyl N-[(1S)-2-(1,3-benzothiazol-2-yl)-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl]ethyl]carbamate (150 mg, 346.63 umol) as a colorless oil. MS (ESI) *m/z* 390.1 $[M+H]^+$

Step 4: (3S)-3-[(2S)-2-amino-3-(1,3-benzothiazol-2-yl)-3-oxo-propyl]pyrrolidin-2-one

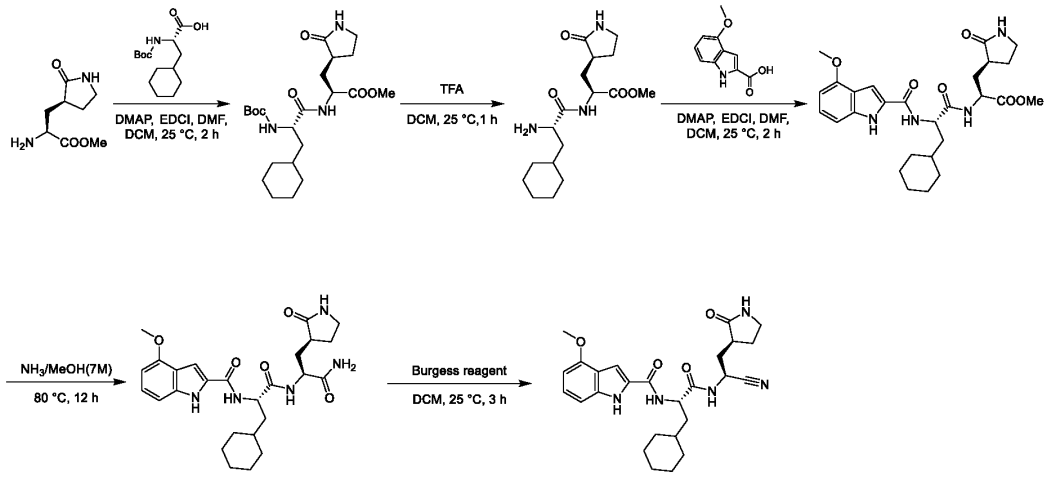
[000223] To a mixture of tert-butyl N-[(1S)-2-(1,3-benzothiazol-2-yl)-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl]ethyl]carbamate (150 mg, 346.63 umol) was added HCl/EtOAc (4 M, 86.66 uL, 1 eq). The resulting mixture was stirred at 20 °C for 2 h, and then concentrated under reduced pressure to give a residue (3S)-3-[(2S)-2-amino-3-(1, 3-benzothiazol-2-yl)-3-oxo-propyl]pyrrolidin -2-one (100 mg, crude) as an oil which was directly used in the next step. MS (ESI) *m/z* 290.1 $[M+H]^+$

Step 5: N-[(1S)-1-[[(1S)-2-(1,3-benzothiazol-2-yl)-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000224] To a mixture of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (18.93 mg, 62.21 umol, 1 eq) in DMF (1 mL) was added 1-methylimidazole (25.54 mg, 311.04 umol, 24.79 uL, 5 eq) and [chloro(dimethylamino)methylene]-dimethyl-ammonium hexafluorophosphate (20.95 mg, 74.65 umol, 1.2 eq) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, and

then added with (3S)-3-[(2S)-2-amino-3-(1,3-benzothiazol-2-yl)-3-oxo-propyl]pyrrolidin-2-one (18 mg, 62.21 umol, 1 eq). The resulting mixture was stirred at 25 °C for 2 h. Once the reaction was completed, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude was purified by neutral prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water(10mMNH4HCO3)- ACN];B%: 35%-65%,10 min) and SFC (column: DAICEL CHIRALCEL OX (250 mm*30 mm,10 um);mobile phase: [0.1% NH_3H_2O MEOH]; B%: 50%-50%,12 min) separation to get the compound N-[(1S)-1-[[(1S)-2-(1,3-benzothiazol-2-yl)-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (8 mg, 13.48 umol) as a solid. MS (ESI) *m/z* 576.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.69 (s, 1H), 8.75 - 8.51 (m, 2H), 8.08 (d, *J*=7.9 Hz, 1H), 7.95 (d, *J*=8.2 Hz, 1H), 7.68 (s, 1H), 7.50 (t, *J*=7.4 Hz, 1H), 7.44 - 7.37 (m, 1H), 7.19 - 7.07 (m, 4H), 6.93 (d, *J*=8.2 Hz, 1H), 6.49 (d, *J*=7.7 Hz, 1H), 3.89 (s, 3H), 3.15 - 2.99 (m, 2H), 2.46 - 2.30 (m, 1H), 2.21 - 1.94 (m, 4H), 1.93 - 1.74 (m, 1H), 1.57 - 1.40 (m, 2H), 0.83 - 0.71 (m, 6H).

Example 6. Synthesis of viral protease inhibitor compound 185



Step 1: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclohexylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000225] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (170 mg, 763.47 umol, 1 eq, HCl) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-propanoic acid (207.17 mg, 763.47 umol, 1 eq) in DMF (2 mL) was added DMAP

(186.55 mg, 1.53 mmol, 2 eq) and EDCI (292.71 mg, 1.53 mmol, 2 eq). The mixture was added DCM (3 mL) and stirred at 25 °C for 2 h. LCMS showed the reaction was completed, and desired MS was observed. The reaction mixture was quenched by addition H_2O (30 mL) at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/EtOAc= 0/1) to get the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 568.77 umol, 74.50% yield) was obtained as a solid. MS (ESI) *m/z* 440.3 $[M+H]^+$

Step 2: (S)-methyl 2-((S)-2-amino-3-cyclohexylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000226] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 455.02 umol, 1 eq) in EtOAc (0.5 mL) was added drop-wise HCl/EtOAc (4 M, 2.00 mL, 17.58 eq) at 25 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product methyl (2S)-2-[[(2S)-2-amino-3-cyclohexyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, crude, HCl) was obtained as a solid and used directly next step. MS (ESI) *m/z* 340.1 $[M+H]^+$

Step 3: ((S)-methyl 2-((S)-3-cyclohexyl-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000227] A solution of 4-methoxy-1H-indole-2-carboxylic acid (99.18 mg, 518.77 umol, 1.3 eq) and methyl (2S)-2-[[(2S)-2-amino-3-cyclohexyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 399.05 umol, 1 eq, HCl) in DMF (2 mL) was added DMAP (97.50 mg, 798.11 umol, 2.0 eq) and EDCI (153.00 mg, 798.11 umol, 2 eq). The mixture was added DCM (4 mL) and stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (20 mL) at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1:0 to 10:1) to get a product methyl (2S)-2-[[(2S)-3-cyclohexyl-2-[(4-methoxy-1H-indole-2-

carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 292.63 umol, 73.33% yield) was obtained as a solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 7.26 (s, 1H), 7.09-7.20 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 4.66 (br dd, J = 9.0, 6.3 Hz, 1H), 4.52-4.58 (m, 1H), 3.93 (s, 3H), 3.72 (s, 3H), 3.22-3.29 (m, 2H), 2.54-2.62 (m, 1H), 2.26-2.33 (m, 1H), 2.15-2.23 (m, 1H), 1.66-1.87 (m, 9H), 1.47-1.54 (m, 1H), 1.25-1.40 (m, 3H), 0.96-1.06 (m, 2H)

Step 4: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000228] A solution of methyl (2S)-2-[[(2S)-3-cyclohexyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 292.63 umol, 1 eq) in ammonia (15.30 g, 898.39 mmol, 15.00 mL, 3070.07 eq) was heated at 80 °C for 12 hours in a sealed tube . The reaction mixture was concentrated under reduced pressure to get a product N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclohexylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (140 mg, crude) was obtained as a solid. MS (ESI) *m/z* 498.2 $[M+H]^+$

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 7.27-7.34 (m, 1H), 7.13-7.20 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 4.62 (t, *J* = 7.6 Hz, 1H), 4.42-4.51 (m, 1H), 3.95 (s, 3H), 3.22-3.30 (m, 2H), 2.53 (td, *J* = 9.2, 4.5 Hz, 1H), 2.33 (ddd, *J* = 9.2, 6.4, 3.4 Hz, 1H), 2.17 (ddd, *J* = 14.1, 11.4, 4.6 Hz, 1H), 1.71-1.88 (m, 9H), 1.46-1.53 (m, 1H), 1.21-1.32 (m, 3H), 0.97-1.09 (m, 2H)

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

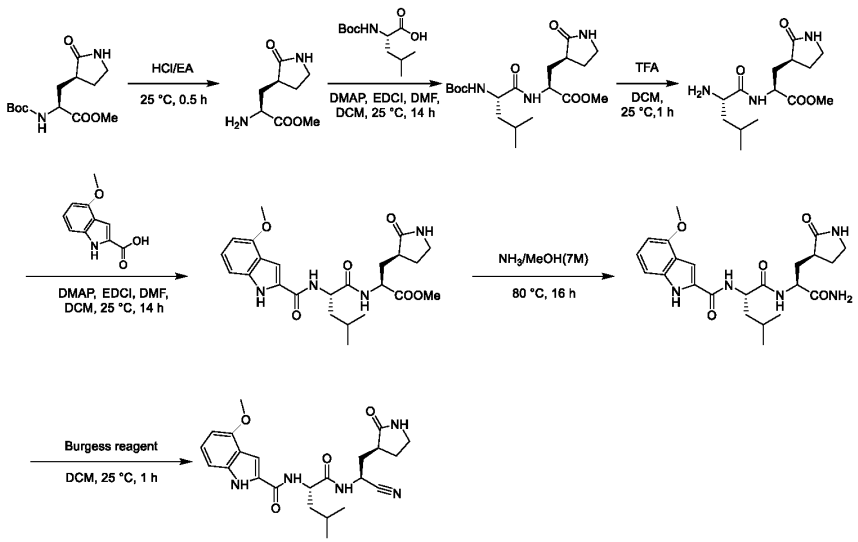
[000229] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclohexylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (80 mg, 160.78 umol, 1 eq) in DCM (3 mL) was added Burgess reagent (114.94 mg, 482.33 umol, 3 eq), and then the resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC to give a product N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclohexylmethyl)-2-oxo-ethyl]-4-methoxy-

1H-indole-2-carboxamide (20.02 mg, 41.75 umol) was obtained as a solid. MS (ESI) *m/z* 480.1 $[M+H]^+$.

Prep-HPLC condition: column: Waters Xbridge BEH C18 100*25mm*5 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-60%,10 min

^1H NMR (METHANOL-d_4, 400 MHz): δ ppm 7.28 (s, 1H), 7.11-7.18 (m, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 10.1, 5.9 Hz, 1H), 4.56-4.61 (m, 1H), 3.93 (s, 3H), 3.22-3.30 (m, 2H), 2.55-2.66 (m, 1H), 2.23-2.40 (m, 2H), 1.65-1.94 (m, 9H), 1.41-1.52 (m, 1H), 1.17-1.36 (m, 3H), 0.94-1.10 (m, 2H).

Example 7. Synthesis of viral protease inhibitor compound 101



Step 1: Methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride

[000230] Methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.75 mmol, 1 eq) was added HCl/EtOAc (4 M, 10 mL, 22.91 eq) at 25 °C. The mixture was stirred at 25 °C for 0.5 h. The resulting mixture was concentrated under reduced pressure to give a product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride (300 mg, 1.28 mmol, 73.29% yield, 95% purity) as a solid and used directly next step. MS (ESI) *m/z* 187.1 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2- oxopyrrolidin-3-yl]propanoate

[000231] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride (157.89 mg, 673.65 umol, 95% purity, 1 eq) and (2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoic acid (155.81 mg, 673.65 umol, 1 eq) in DMF (2 mL) was added EDCI (258.28 mg, 1.35 mmol, 2 eq) and DMAP (164.60 mg, 1.35 mmol, 2 eq). The mixture was added DCM (3 mL) and stirred at 25 °C for 14 h. The resulting mixture was diluted with H_2O (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, petroleum ether/EtOAc=3/1 to 1/1) to get the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 500.65 umol, 74.32% yield, 80% purity) was obtained as a solid. MS (ESI) *m/z* 400.3 $[M+H]^+$

Step 3: (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-pentanamide

[000232] tert-butylN-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl] carbamate (200 mg, 491.19 umol, 90% purity, 1 eq) in DCM (5 mL) was added TFA (770.00 mg, 6.75 mmol, 0.5 mL, 13.75 eq) at 25 °C. The mixture was stirred at 25 °C for 1 h. The resulting mixture was concentrated under reduced pressure to give a product (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl] ethyl]-4-methyl-pentanamide (120 mg, 405.50 umol, 82.55% yield, 90% purity) as an oil and used directly next step. MS (ESI) *m/z* 300.2 $[M+H]^+$

Step 4: methyl(2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000233] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (120 mg, 627.67 umol, 1 eq) and methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (208.78 mg, 627.67 umol, 90% purity, 1 eq) in DCM (1 mL) was added EDCI (240.65 mg, 1.26 mmol, 2 eq) and DMAP (153.36 mg, 1.26 mmol, 2 eq). The mixture was added DMF (0.5 mL) and stirred at 25 °C for 14 h. The resulting mixture was diluted with H_2O (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by

column chromatography (SiO2, petroleum ether/EtOAc=3/1 to 0/1) to get the compound methyl(2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (160 mg, 304.74 umol, 48.55% yield, 90% purity) as a solid. MS (ESI) *m/z* 473.3 $[M+H]^+$

Step 5: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000234] methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]3- [(3S)-2-oxopyrrolidin-3-yl]propanoate (180 mg mg, 342.83 umol, 90% purity, 1 eq) was added NH_3/MeOH (7 M, 54.00 mL, 1102.58 eq), The mixture was stirred at 80 °C for 16 h. The resulting mixture was concentrated under reduced pressure to give a residue N-[(1S)-1-[[(1S)-2-amino-2-oxo-1- [[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (130 mg, 255.73 umol, 74.59% yield, 90% purity) as an oil. MS (ESI) *m/z* 458.3 $[M+H]^+$

[000235] 1H NMR (400 MHz, METHANOL-d4) δ ppm 0.97- 1.02 (dd, J=14.55, 6.11 Hz, 6 H) 1.74 - 1.82 (m, 5 H) 2.15 (ddd, J=14.03, 11.34, 4.58 Hz, 1 H) 2.25 - 2.37 (m, 1 H) 2.52 (ddt, J=13.82, 9.41, 4.71, 4.71 Hz, 1 H) 3.17 - 3.29 (m, 2 H) 3.90 (s, 3 H) 4.46 (dd, J=11.25, 4.16 Hz, 1 H) 4.60 (dd, J=9.66, 5.01 Hz, 1 H) 6.50 - 6.52 (d, J=7.70 Hz, 1 H) 7.02 - 7.04 (d, J=8.31 Hz, 1 H) 7.15 - 7.17 (m, 1 H) 7.28 - 7.29 (d, J=0.73 Hz, 1 H)

Step 6: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl-3-methyl-butyl
-4-methoxy-1H-indole-2-carboxamide

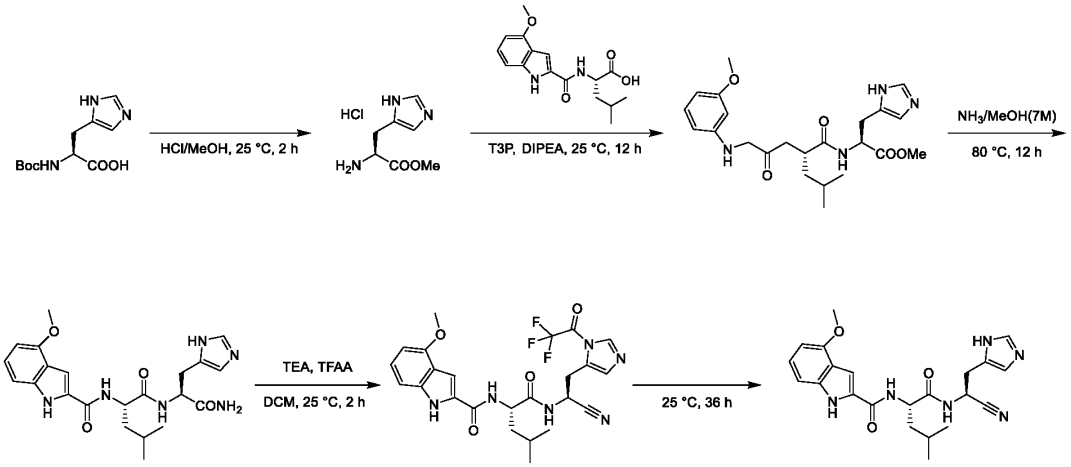
[000236] To a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (100 mg, 196.71 umol, 90% purity, 1 eq) in DCM (4 mL) was added Burgess reagent (93.75 mg, 393.42 umol, 2 eq). The mixture was stirred at 25 °C for 1 h. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC to get the product N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin -3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (23 mg, 49.50 umol, 25.16% yield, 94.59% purity) as a solid. MS (ESI) *m/z* 440.1 $[M+H]^+$.

Prep-HPLC condition:

column:Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water(10 mM NH4HCO3)-ACN];B%: 27%-57%,10 min

[000237] 1H NMR (400 MHz, DMSO-d6) δ ppm 0.88 - 0.94 (m, 6 H) 1.67 - 1.74 (m, 5 H) 2.11 - 2.13 (m, 2 H) 2.14 - 2.34 (m, 1 H) 3.09 - 3.14 (m, 2 H) 3.88 (s, 3 H) 4.36 - 4.57 (m, 1 H) 4.90 - 5.00 (m, 1 H) 6.49 - 6.51 (d, J=7.58 Hz, 1 H) 6.99 - 7.01 (m, 2 H) 7.38 (s, 1 H) 7.70 (s, 1 H) 8.45 - 8.47 (br d, J=7.70 Hz, 1 H) 8.89 - 8.91 (br d, J=7.95 Hz, 1 H) 11.57 (br s, 1 H)

Example 8. Synthesis of viral protease inhibitor compound 593



Step 1: methyl (2S)-2-amino-3-(1H-imidazol-5-yl) propanoate

[000238] To the solution of (2S)-2-(tert-butoxycarbonylamino)-3-(1H-imidazol-5-yl)propanoic acid (0.5 g, 1.96 mmol, 1 *eq*) in MeOH (0.6 mL) was added HCl/MeOH (4 M, 4.90 mL, 10 *eq*) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to get the product. Methyl (2S)-2-amino-3-(1H-imidazol-5-yl) propanoate (400 mg, crude, HCl) was obtained as a solid and used directly next step. MS (ESI) *m/z* 170.1 $[M+H]^+$

Step 2: methyl (2S)-3-(1H-imidazol-5-yl)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino] -4-methyl-pentanoyl]amino]propanoate

[000239] To a mixture of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (741.86 mg, 1.77 mmol, 1 *eq*, TFA) and methyl (2S)-2-amino-3-(1H-imidazol-5-yl)propanoate (0.3 g, 1.77 mmol, 1 *eq*, HCl), DIPEA (1.15 g, 8.87 mmol, 1.54

mL, 5 *eq*) in THF (0.3 mL) and DCM (0.3 mL) was added T3P (1.69 g, 2.66 mmol, 1.58 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was washed with brine (3 mL * 3) and dried over anhydrous sodium sulfate and concentrated to get the crude product. Methyl (2S)-3-(1H-imidazol-5-yl)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino] -4-methyl-pentanoyl]amino]propanoate (300 mg, crude) was obtained as a solid and used directly next step. MS (ESI) *m/z* 456.2 $[M+H]^+$

[000240] 1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.48 (s, 1 H), 7.27 (s, 1 H), 7.11 - 7.18 (m, 1 H), 7.02 (d, J = 8.16 Hz, 1 H), 6.85 (s, 1 H), 6.51 (d, J = 7.72 Hz, 1 H), 4.60 - 4.71 (m, 2 H), 3.93 (s, 3 H), 3.68 (s, 3 H), 3.00 - 3.17 (m, 3 H), 1.62 - 1.78 (m, 3 H), 0.97 (dd, J = 13.78, 6.06 Hz, 6 H)

Step 3: N-[(1S)-1-[[(1S)-2-amino- 1-(1H-imidazol-5-ylmethyl)-2-oxo-ethyl]carbamoyl]-3-methyl-butyl] -4-methoxy-1H-indole-2-carboxamide

[000241] To methyl (2S)-3-(1H-imidazol-5-yl)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]propanoate (200 mg, 439.07 umol, 1 *eq*) was added NH_3/MeOH (7 M, 11.76 mL, 187.56 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C and stirred for 12 h. The reaction mixture was cooled to 25 °C and concentrated to get the crude product. N-[(1S)-1-[[(1S)-2-amino-1-(1H-imidazol-5-ylmethyl)-2-oxo-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (170 mg, 378.83 umol, 86.28% yield, 98.16% purity) was obtained as a solid and used directly next step. MS (ESI) *m/z* 441.2 $[M+H]^+$

Step 4: N-[(1S)-1-[[(1S)-1-cyano-2-(1H-imidazol-5-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy- 1H-indole-2-carboxamide

[000242] To a mixture of N-[(1S)-1-[[(1S)-2-amino-1-(1H-imidazol-5-ylmethyl)-2-oxo-ethyl]carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (140 mg, 317.82 umol, 1 *eq*) in DCM (2 mL) was added TFAA (133.51 mg, 635.65 umol, 88.41 uL, 2 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to get the crude product. Crude product turned into compound 593 after 36 h in storage. The residue was purified by prep-HPLC. N-[(1S)-1-[[(1S)-1-cyano-2-(1H-imidazol-5-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

(23.89 mg, 56.31 umol, 17.72% yield, 99.581% purity) was obtained as a solid. MS (ESI) *m/z* 423.2 $[M+H]^+$

Prep-HPLC condition:
column: Waters Xbridge BEH C18 100*25mm*5 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 25%-55%,10 min

[000243] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.58 (s, 1 H), 7.30 (s, 1 H), 7.12 - 7.21 (m, 1 H), 6.99 - 7.09 (m, 2 H), 6.52 (d, *J* = 7.72 Hz, 1 H), 5.05 (t, *J* = 7.06 Hz, 1 H), 4.61 (br dd, *J* = 9.70, 4.85 Hz, 1 H), 3.94 (s, 3 H), 3.06 - 3.21 (m, 2 H), 1.60 - 1.83 (m, 3 H), 0.99 (dd, *J* = 13.89, 6.17 Hz, 6 H)

Step 5: tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate

[000244] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (5 g, 26.15 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (5.88 g, 31.38 mmol, 1.2 *eq*, HCl), EDCI (6.52 g, 34.00 mmol, 1.3 *eq*), HOBt (4.59 g, 34.00 mmol, 1.3 *eq*) in DMF (30 mL) was added TEA (7.94 g, 78.46 mmol, 10.92 mL, 3 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was added water (90 mL) and extracted with EtOAc (25 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (25 mL) and 5% aqueous solution of sodium bicarbonate (25 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the product. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 30:1 to 10:1). Tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate (5.93 g, 16.45 mmol, 62.91% yield) was obtained as a solid. MS (ESI) *m/z* 361.2 $[M+H]^+$

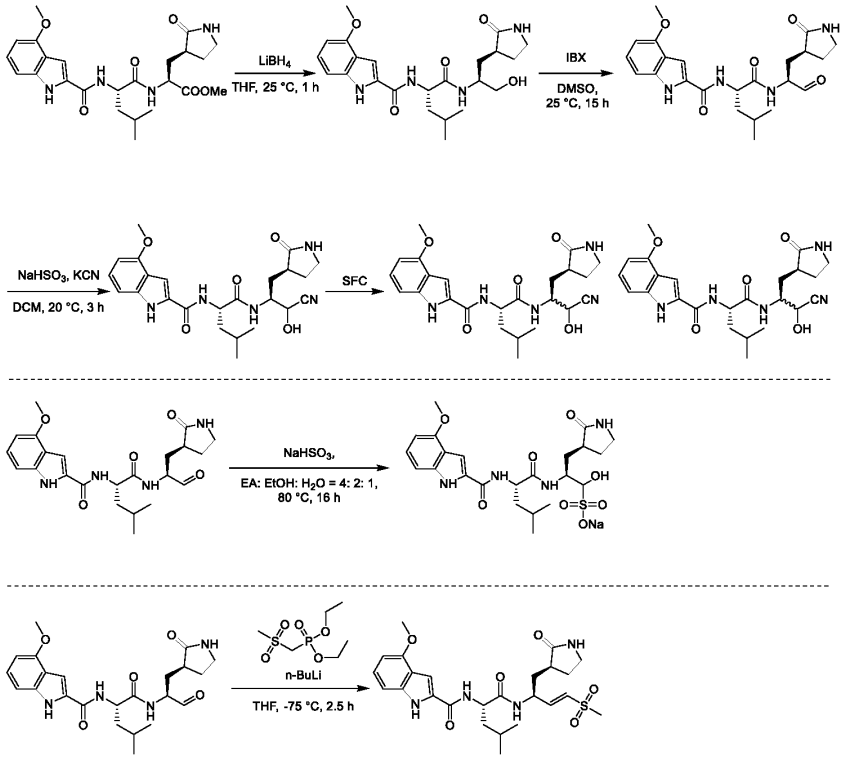
[000245] ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.25 (br s, 1 H), 7.10 - 7.16 (m, 1 H), 6.93 - 7.00 (m, 2 H), 6.56 (br d, *J* = 8.31 Hz, 1 H), 6.44 (d, *J* = 7.70 Hz, 1 H), 4.66 (td, *J* = 8.50, 5.14 Hz, 1 H), 3.88 (s, 3 H), 1.62 - 1.75 (m, 2 H), 1.57 - 1.62 (m, 1 H), 1.42 (s, 9 H), 0.92 (dd, *J* = 6.17, 3.85 Hz, 6 H).

Step 6: (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid

[000246] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (2.00 g, 5.55 mmol, 1 *eq*) in DCM (8 mL) was added TFA (10.27 g, 90.04 mmol, 6.67 mL, 16.23 *eq*) and H_2O (666.67 mg, 37.01 mmol, 666.67 uL, 6.67 *eq*)

in one portion at 0 °C under N_2. The mixture was stirred at 25 °C and stirred for 4 h. The reaction mixture was concentrated to get the crude product. (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (2.24 g, 5.35 mmol, 96.50% yield, TFA) was obtained as a solid and used directly next step. MS (ESI) *m/z* 305.1 $[M+H]^+$

Example 9. Synthesis of viral protease inhibitor compounds 135, 595 and 136



Step 1: N-[(1S)-1-[[(1S)-1-(hydroxymethyl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl -butyl]-4-methoxy-1H-indole-2-carboxamide

[000247] To a mixture of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.5 g, 2.86 mmol, 90% purity, 1 eq) in THF (20 mL) was added $LiBH_4$ (124.45 mg, 5.71 mmol, 2 eq). The mixture was stirred at 25 °C for 2 h. Once the reaction was completed, the reaction mixture was quenched by addition H_2O (10 mL) at 0 °C, and extracted with EtOAc (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue compound N-[(1S)-1-[[(1S)-1-(hydroxymethyl)-2-[(3S)-2-oxopyrrolidin-3-

yl]ethyl]carbamoyl]-3- methyl- butyl]-4-methoxy-1H-indole-2-carboxamide (1.0 g, 2.25 mmol, 78.74% yield) was obtained as a solid. MS (ESI) m/z 445.1 $[M+H]^+$. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.27 (s, 1H), 7.19 - 7.10 (m, 1H), 7.02 (d, *J*=8.3 Hz, 1H), 6.51 (d, *J*=7.7 Hz, 1H), 4.65 - 4.53 (m, 1H), 4.05 - 3.97 (m, 1H), 3.93 (s, 3H), 3.60 - 3.43 (m, 2H), 3.27 - 3.10 (m, 2H), 2.59 - 2.43 (m, 1H), 2.39 - 2.19 (m, 1H), 2.08 - 1.89 (m, 1H), 1.85 - 1.63 (m, 4H), 1.60 - 1.46 (m, 1H), 1.00 (dd, *J*=6.1, 12.5 Hz, 6H).

Step 2: N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4- methoxy-1H-indole-2-carboxamide

[000248] To a mixture of N-[(1S)-1-[[(1S)-1-(hydroxymethyl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl] -3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (674 mg, 1.52 mmol, 1 eq) in DMSO (25 mL) was added IBX (849.14 mg, 3.03 mmol, 2 eq). The mixture was stirred at 25 °C for 15 h. Once the reaction was completed, the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL * 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was added ethyl acetate (10 mL) and filtered to give the product N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (420 mg, 759.31 umol, 50.08% yield, 80% purity) as a solid. MS (ESI) *m/z* 443.1 $[M+H]^+$. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.27 (s, 1H), 7.20 - 7.09 (m, 1H), 7.02 (d, *J*=8.3 Hz, 1H), 6.51 (d, *J*=7.7 Hz, 1H), 4.60 (dt, *J*=5.5, 9.9 Hz, 1.5H), 4.47 (dd, *J*=1.4, 4.1 Hz, 0.5H), 4.02 - 3.94 (m, 1H), 3.93 (s, 3H), 3.28 - 3.15 (m, 2H), 2.54 - 2.39 (m, 1H), 2.37 - 2.21 (m, 1H), 2.10 - 1.93 (m, 1H), 1.89 - 1.49 (m, 5H), 1.17 - 0.91 (m, 6H).

Step 3: N-[(1S)-1-[[(1S)-2-cyano-2-hydroxy-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl] -3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000249] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl -butyl]-4-methoxy-1H-indole-2-carboxamide (400 mg, 723.15 umol, 80% purity, 1 eq) in DCM (10 mL) was added saturated $NaHSO_3$ (301.01 mg, 2.89 mmol, 203.38 uL, 4 eq). The mixture was stirred at 25 °C for 30 min, and then an aq solution of KCN (42 mg, 644.96 umol, 27.63 uL, 8.92e-1 eq) in H_2O (0.8 mL) was added. The mixture was stirred at 25 °C for 3 h. Once the reaction was completed, the

organic phase was collected and the aqueous layer was extracted with DCM (30 mL * 3). The combined organic phase was washed with brine (30 mL * 2), dried over Na_2SO_4, and concentrated to get the crude. The liquid was added NaOH to pH=9, then quenched by adding aq NaCl, then added NaOH to pH > 14. The crude was purified by HCl prep-HPLC to get the mixture 120 mg, and SFC separation to get compound N-[(1S)-1-[[(1S)-2-cyano-2-hydroxy-1-[[(3S)-2-oxopyrrolidin -3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (34 mg, 70.96 umol, 9.81% yield, 97.99% purity) and compound N-[(1S)-1-[[(1S)-2-cyano-2-hydroxy-1- [[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (64 mg, 131.75 umol, 18.22% yield, 96.66% purity) as a solid. MS (ESI) *m/z* 470.2$[M+H]^+$.

prep-HPLC condition: column: Phenomenex luna C18 80*40 mm*3 um ;mobile phase: [water (0.04% HCl) - ACN];B%: 26%-50%,7min

SFC condition: column: REGIS (R,R)WHELK-O1(25 0mm*25mm, 10 um);mobile phase: [Neu-IPA]; B%: 35%-35%,11 min

[000250] Compound 134 Isomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.57 (d, J=1.8 Hz, 1H), 8.40 (d, *J*=7.9 Hz, 1H), 8.13 (d, *J*=9.3 Hz, 1H), 7.57 (s, 1H), 7.36 (d, *J*=1.5 Hz, 1H), 7.13 - 7.06 (m, 1H), 7.03 - 6.97 (m, 1H), 6.69 (d, *J*=7.3 Hz, 1H), 6.50 (d, *J*=7.7 Hz, 1H), 4.50 - 4.40 (m, 1H), 4.33 (t, *J*=7.8 Hz, 1H), 4.10 - 3.97 (m, 1H), 3.88 (s, 3H), 3.16 - 2.98 (m, 2H), 2.39 - 2.26 (m, 1H), 2.15 - 2.01 (m, 1H), 1.92 - 1.80 (m, 1H), 1.80 - 1.63 (m, 2H), 1.62 - 1.40 (m, 3H), 0.90 (dd, *J*=6.3, 15.5 Hz, 6H).

[000251] Compound 134 Isomer 2: ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.55 (br d, *J*=1.5 Hz, 1H), 8.35 (d, *J*=7.9 Hz, 1H), 8.21 (d, *J*=8.6 Hz, 1H), 7.60 (s, 1H), 7.34 (d, *J*=1.8 Hz, 1H), 7.12 - 7.06 (m, 1H), 7.03 - 6.97 (m, 1H), 6.64 (d, *J*=6.0 Hz, 1H), 6.50 (d, *J*=7.5 Hz, 1H), 4.60 - 4.49 (m, 2H), 4.12 - 3.96 (m, 1H), 3.88 (s, 3H), 3.19 - 2.98 (m, 2H), 2.41 - 2.26 (m, 1H), 2.16 - 1.95 (m, 2H), 1.92 - 1.35 (m, 5H), 0.98 - 0.82 (m, 6H).

Step 4: [(2S)-1-hydroxy-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propyl]sulfonyloxysodium

[000252] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl- butyl]-4-methoxy-1H-indole-2-carboxamide (50 mg, 112.99 umol, 1 eq) in EtOH (0.4 mL)， EtOAc (0.2 mL) and H_2O (0.1 mL) was added

$NaHSO_3$ (11.76 mg, 112.99 umol, 7.94 uL, 1 eq). The mixture was stirred at 80 °C for 16 h. Once the reaction was completed, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was added DCM (3 mL) and ACN (3 mL), filtered to get the compound [(2S)-1-hydroxy-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4- methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propyl]sulfonyloxysodium (5 mg, 5.26 umol, 4.66% yield, 57.5% purity) as a solid. (ESI) *m/z* 525.1 $[M+H]^+$

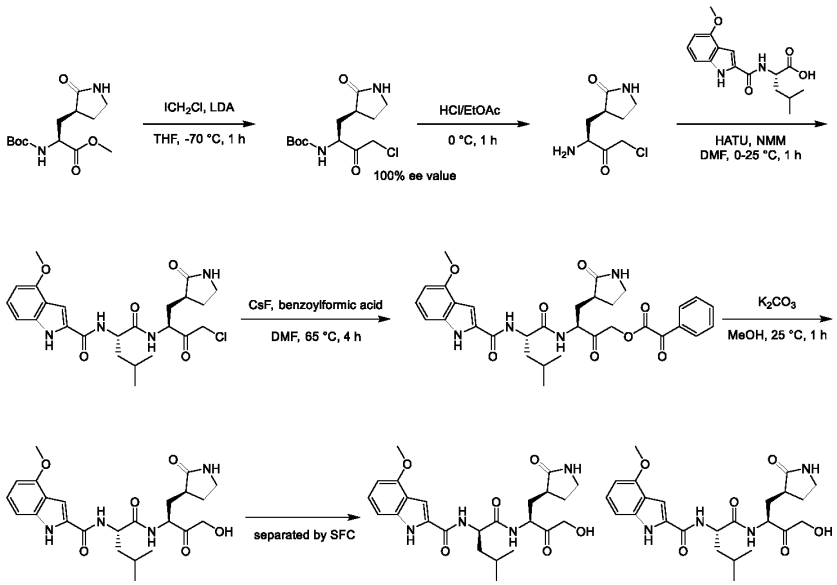
[000253] ^1H NMR (400MHz, DMSO-*d6*) δ = 11.67 - 11.44 (m, 1H), 9.42 (s, 0.02H), 8.52 - 8.27 (m, 1H), 7.74 - 7.59 (m, 1H), 7.43 (s, 1H), 7.32 (dd, *J*=1.8, 4.9 Hz, 1H), 7.15 - 6.93 (m, 2H), 6.50 (d, *J*=7.7 Hz, 1H), 5.40 - 5.24 (m, 1H), 4.61 - 4.33 (m, 1H), 4.31 - 4.15 (m, 0.5H), 4.11 - 3.96 (m, 0.5H), 3.94 (dd, *J*=2.4, 5.7 Hz, 0.5H), 3.88 (s, 3H), 3.85 - 3.81 (m, 0.5H), 3.19 - 2.94 (m, 2H), 2.27 - 1.87 (m, 3H), 1.85 - 1.42 (m, 5H), 0.99 - 0.79 (m, 6H)

Step 5: 4-methoxy-N-[(1S)-3-methyl-1-[[(E,1S)-3-methylsulfonyl-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] allyl]carbamoyl]butyl]-1H-indole-2-carboxamide

[000254] To a mixture of 1-[ethoxy(methylsulfonylmethyl)phosphoryl]oxyethane (130.06 mg, 564.96 umol, 5 eq) in THF (2 mL) was added n-BuLi (2.5 M, 180.79 uL, 4 eq) at 0 °C under N_2. The mixture was stirred at -75 °C for 30 min, then added N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (50 mg, 112.99 umol, 1 eq). The mixture was stirred at -75 °C for 2 h. Once the reaction was completed, the reaction mixture was quenched by addition H_2O (10 mL) at 0 °C, and then concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to get the compound 4-methoxy-N-[(1S)-3-methyl -1-[[(E,1S)-3-methylsulfonyl-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]allyl]carbamoyl]butyl]-1H-indole-2-carboxamide (15 mg, 28.82 umol, 25.50% yield, 99.638% purity) as a solid. (ESI) *m/z* 519.1 $[M+H]^+$ column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.04%HCl)-ACN];B%: 26%-52%,7min

[000255] ^1H NMR (400MHz, METHANOL-d_4) δ = 7.33 - 7.26 (m, 1H), 7.20 - 7.10 (m, 1H), 7.03 (d, *J*=8.3 Hz, 1H), 6.85 (dd, *J*=4.8, 15.3 Hz, 1H), 6.68 (dd, *J*=1.6, 15.3 Hz, 1H), 6.52 (d, *J*=7.7 Hz, 1H), 4.77 - 4.67 (m, 1H), 4.61 - 4.50 (m, 1H), 3.99 - 3.83 (m, 3H), 3.28 - 3.18 (m, 2H), 3.01 - 2.88 (m, 3H), 2.65 - 2.50 (m, 1H), 2.39 - 2.22 (m, 1H), 2.15 - 1.97 (m, 1H), 1.91 - 1.62 (m, 5H), 1.09 - 0.92 (m, 6H)

Example 10. Synthesis of viral protease inhibitor compound 740 and 741



Step 1: tert-butyl ((S)-4-chloro-3-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)carbamate

[000256] To a solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.6 g, 2.10 mmol, 1 *eq*) in THF (24 mL) was added chloro(iodo)methane (1.48 g, 8.38 mmol, 608.42 uL, 4 *eq*), then the solution was cooled to -70 °C and LDA (2 M, 6.29 mL, 6 *eq*) was added drop-wise. The reaction was stirred at -70 °C for 1 h. Upon completion, the reaction mixture was quenched by addition a mixture of AcOH (4.5 mL) and THF (22 mL) at -70 °C, and then diluted with ethyl acetate (50 mL) and extracted with water (30 mL * 2), sat. $NaHCO_3$ (30 mL). The organic layers were washed dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 2:1 to 0:1) and then triturated with methyl tertiary butyl ether:petroleum ether = 4:1 (3 mL) to give tert-butyl N-[(1S)-3-chloro-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]propyl]carbamate (0.35 g, 1.03 mmol, 49.32% yield, 90% purity) as a solid. MS (ESI) *m/z* 308.0 $[M+H]^+$.

[000257] ^1H NMR (400 MHz, DMSO-d_6) δ = 7.66 (br s, 1H), 7.53 (br d, *J* = 7.7 Hz, 1H), 4.61 (d, *J* = 2.2 Hz, 2H), 4.22 - 4.10 (m, 1H), 3.21 - 3.11 (m, 2H), 2.34 - 2.06 (m, 2H), 1.93 - 1.80 (m, 1H), 1.73 - 1.54 (m, 2H), 1.39 (s, 9H).

Step 2: (S)-3-((S)-2-amino-4-chloro-3-oxobutyl)pyrrolidin-2-one

[000258] A solution of tert-butyl N-[(1S)-3-chloro-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]propyl]carbamate (0.33 g, 1.08 mmol, 1 *eq*) in HCl/EtOAc (4 M, 5 mL, 18.47 *eq*) was stirred at 0 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (3S)-3-[(2S)-2-amino-4-chloro-3-oxo-butyl]pyrrolidin-2-one (0.3 g, crude, HCl) as an oil. MS (ESI) *m/z* 205.0 $[M+H]^+$.

[000259] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.75 (br s, 3H), 7.97 (br s, 1H), 4.96 - 4.91 (m, 1H), 4.77 (s, 1H), 4.37 - 4.23 (m, 1H), 3.26 - 3.07 (m, 2H), 2.60 (br d, *J* = 8.6 Hz, 1H), 2.37 - 2.27 (m, 1H), 1.96 - 1.90 (m, 1H), 1.79 - 1.66 (m, 1H).

Step 3: N-((S)-1-(((S)-4-chloro-3-oxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000260] A solution of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (416.53 mg, 1.37 mmol, 1.1 *eq*) in DMF (5 mL) was added HATU (946.18 mg, 2.49 mmol, 2 *eq*) and NMM (251.71 mg, 2.49 mmol, 273.59 uL, 2 *eq*), the solution was stirred at 0 °C for 0.5 h. Then a solution of (3S)-3-[(2S)-2-amino-4-chloro-3-oxo-butyl]pyrrolidin-2-one (0.3 g, 1.24 mmol, 1 *eq*, HCl) in DMF (5 mL) was added drop-wise at 0 °C. The reaction was stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was diluted with water (50 mL) at 0 °C drop-wise and extracted with EtOAc (20 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 2:1 to 0:1). To give N-[(1S)-1-[[(1S)-3-chloro-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]propyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (0.3 g, 549.92 umol, 44.20% yield, 90% purity) as a solid. MS (ESI) *m/z* 491.1 $[M+H]^+$.

[000261] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.58 (br s, 1H), 8.74 - 8.57 (m, 1H), 8.44 (br d, *J* = 5.0 Hz, 1H), 7.65 (br d, *J* = 4.5 Hz, 1H), 7.37 (br s, 1H), 7.15 - 7.06 (m, 1H), 7.01 (br d, *J* = 8.1 Hz, 1H), 6.50 (br d, *J* = 7.6 Hz, 1H), 4.75 - 4.60 (m, 1H), 4.59 - 4.55 (m, 1H), 4.44 (br d, *J* = 9.2 Hz, 2H), 3.88 (s, 3H), 3.13 - 3.01 (m, 2H), 2.34 - 2.18 (m, 1H), 2.09 (br dd, *J* = 2.5, 3.9 Hz, 1H), 1.99 - 1.90 (m, 1H), 1.78 - 1.49 (m, 5H), 0.97 - 0.81 (m, 6H).

Step 4: (S)-3-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-2-oxo-4-((S)-2-oxopyrrolidin-3-yl)butyl 2-oxo-2-phenylacetate

[00262] To a solution of N-[(1S)-1-[[(1S)-3-chloro-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]propyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (0.25 g, 509.19 umol, 1 *eq*) in DMF (6 mL) was added benzoylformic acid (99.38 mg, 661.94 umol, 1.3 *eq*) and CsF (177.89 mg, 1.17 mmol, 43.18 uL, 2.3 *eq*). The reaction was stirred at 65 °C for 4 h under N_2 atmosphere. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give [(3S)-3-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-2-oxo-4-[(3S)-2-oxopyrrolidin-3-yl]butyl] 2-oxo-2-phenyl-acetate (0.3 g, crude) as an oil. MS (ESI) *m/z* 605.2 $[M+H]^+$.

Step 5&6: N-[(1R)-1-[[(1S)-3-hydroxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]propyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide N-[(1S)-1-[[(1S)-3-hydroxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]propyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[00263] To a solution of [(3S)-3-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-2-oxo-4-[(3S)-2-oxopyrrolidin-3-yl]butyl] 2-oxo-2-phenyl-acetate (0.3 g, 496.16 umol, 1 *eq*) in MeOH (10 mL) was added K_2CO_3 (3.43 mg, 24.81 umol, 0.05 *eq*). The reaction was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give the product.

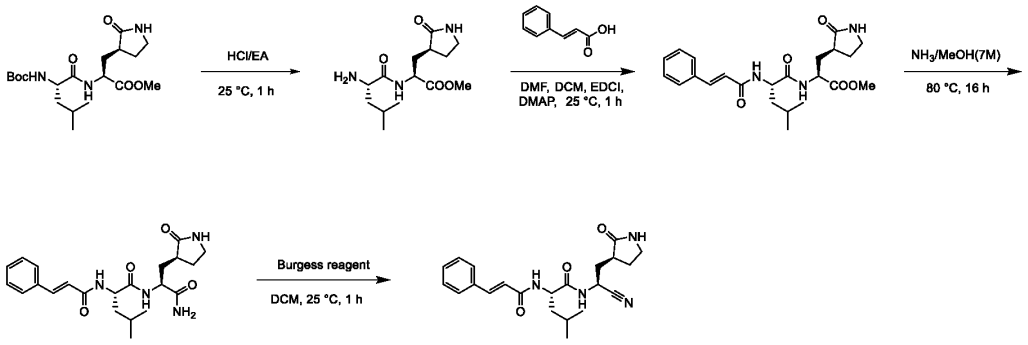
[00264] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.58 (s, 1H), 8.50 (d, *J* = 7.8 Hz, 1H), 8.41 (d, *J* = 7.9 Hz, 1H), 7.63 (s, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 7.14 - 7.05 (m, 1H), 7.04 - 6.94 (m, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 5.05 - 4.98 (m, 1H), 4.57 - 4.46 (m, 1H), 4.41 (ddd, *J* = 4.0, 7.7, 11.2 Hz, 1H), 4.34 - 4.25 (m, 1H), 4.22 - 4.13 (m, 1H), 3.88 (s, 3H), 3.18 - 3.01 (m, 2H), 2.25 - 2.14 (m, 1H), 2.13 - 2.04 (m, 1H), 1.99 - 1.84 (m, 1H), 1.77 - 1.48 (m, 5H), 0.93 (br d, *J* = 6.2 Hz, 3H), 0.89 (br d, *J* = 6.4 Hz, 3H).

[00265] To give N-[(1S)-1-[[(1S)-3-hydroxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]propyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (23.86 mg, 49.08 umol, 9.89% yield, 97.2% purity) as a solid. MS (ESI) *m/z* 473.2

$[M+H]^+$. The product was separated by chiral-SFC (column: DAICEL CHIRALCEL OJ(250mm*30mm,10um);mobile phase: [Neu-MeOH];B%: 20%-20%,15min) to give N-[(1R)-1-[[(1S)-3-hydroxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]propyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (15.43 mg, 31.22 umol, 6.29% yield, 95.6% purity) as a solid. MS (ESI) *m/z* 473.2 $[M+H]^+$.

[000266] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.57 (s, 1H), 8.45 (br d, *J* = 8.1 Hz, 1H), 8.41 (br d, *J* = 7.8 Hz, 1H), 7.62 (s, 1H), 7.36 (d, *J* = 1.3 Hz, 1H), 7.14 - 7.05 (m, 1H), 7.04 - 6.97 (m, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 5.06 (br s, 1H), 4.62 - 4.38 (m, 2H), 4.30 - 4.19 (m, 1H), 4.19 - 4.09 (m, 1H), 3.88 (s, 3H), 3.19 - 3.01 (m, 2H), 2.37 - 2.22 (m, 1H), 2.09 (br dd, *J* = 3.2, 6.2 Hz, 1H), 1.99 - 1.86 (m, 1H), 1.80 - 1.43 (m, 5H), 0.94 (d, *J* = 6.2 Hz, 3H), 0.89 (d, *J* = 6.2 Hz, 3H).

Example 11. Synthesis of viral protease inhibitor compound 143



Step 1: methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000267] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 625.81 umol, 1 *eq*) was added HCl/EtOAc (8 mL) at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue get a product methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (230 mg, crude) as an oil. MS (ESI) *m/z* 300.0 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000268] A mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (230 mg, 684.88 umol, 1 *eq*, HCl) and (E)-3-phenylprop-2-enoic acid (202.94 mg, 1.37 mmol, 162.35 uL, 2 *eq*) in DMF (2 mL) and DCM (4 mL), and added EDCI (262.59 mg, 1.37 mmol, 2 *eq*) and DMAP (167.34 mg, 1.37 mmol, 2 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (SiO_2, petroleum ether:EtOAc= 1:1) to get a product methyl (2S)-2-[[(2S)-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 465.65 umol, 67.99% yield) as an oil. MS (ESI) *m/z* 430.1 $[M+H]^+$.

Step 3: (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanamide

[000269] A mixture of methyl (2S)-2-[[(2S)-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 465.65 umol, 1 *eq*) in NH_3/MeOH (7 M, 7 mL, 97% purity, 105.23 *eq*) heated to 80 °C for 16 h in the sealed tube. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue to get the product (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanamide (200 mg, crude) as an oil. MS (ESI) *m/z* 415.1 $[M+H]^+$.

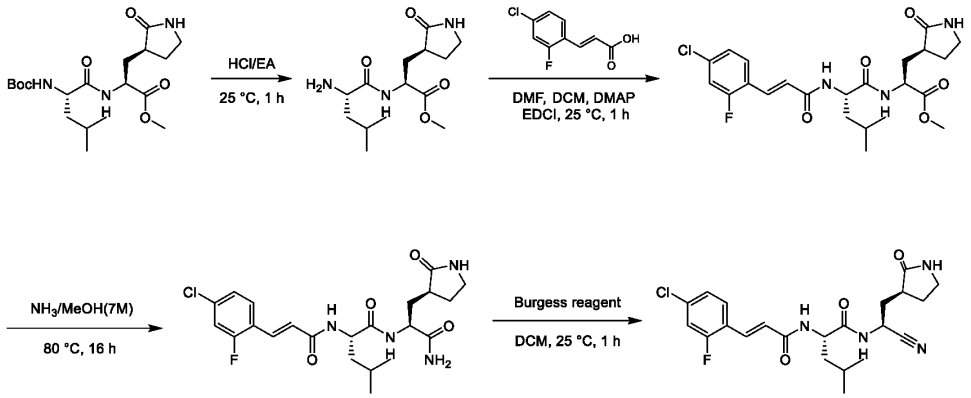
Step 4: (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanamide

[000270] A mixture of (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanamide (200 mg, 482.51 umol, 1 *eq*) in DCM (2 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (574.93 mg, 2.41 mmol, 5 *eq*), the mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 25% - 55%, 8min) to give a product (2S)-N-[(1S)-1-cyano-2-[(3S)-2-

oxopyrrolidin-3-yl]ethyl]-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanamide (23.1 mg, 58.26 umol, 12.07% yield, 100% purity) as a solid. MS (ESI) *m/z* 397.2 $[M+H]^+$.

[000271] ^1H NMR (400MHz, $CDCl_3$) = 8.70 (br d, J=6.6 Hz, 1H), 7.66 - 7.55 (m, 1H), 7.54 - 7.44 (m, 2H), 7.35 (br s, 3H), 6.72 - 6.52 (m, 2H), 6.47 (d, J=15.7 Hz, 1H), 5.02 - 4.67 (m, 2H), 3.49 - 3.22 (m, 2H), 2.56 - 2.27 (m, 3H), 2.02 - 1.88 (m, 1H), 1.88 - 1.80 (m, 1H), 1.75 - 1.61 (m, 3H), 1.07 - 0.87 (m, 6H)

Example 12. Synthesis of viral protease inhibitor compound 598



Step 1: methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000272] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 750.98 umol, 1 *eq*) was added HCl/EtOAc (4 M, 6 mL, 31.96 *eq*) at 25 °C for 1 h. Upon completion, the product blow-dried directly with N_2 to get the product methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (260 mg, crude) as an oil. MS (ESI) *m/z* 300.1 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-2-[[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000273] A mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 744.43 umol, 1 *eq*, HCl) and (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoic acid (298.66 mg, 1.49 mmol, 81.96 uL, 2 *eq*) in DMF (2 mL) and DCM (4 mL) was added EDCI (285.42 mg, 1.49 mmol, 2 *eq*) and DMAP

(181.89 mg, 1.49 mmol, 2 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (SiO_2, petroleum ether:EtOAc= 0:1) to get a product methyl (2S)-2-[[(2S)-2-[[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (80 mg, 165.99 umol, 22.30% yield) as an oil. MS (ESI) *m/z* 482.1 $[M+H]^+$.

Step 3: (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-[[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]amino]-4-methyl-pentanamide

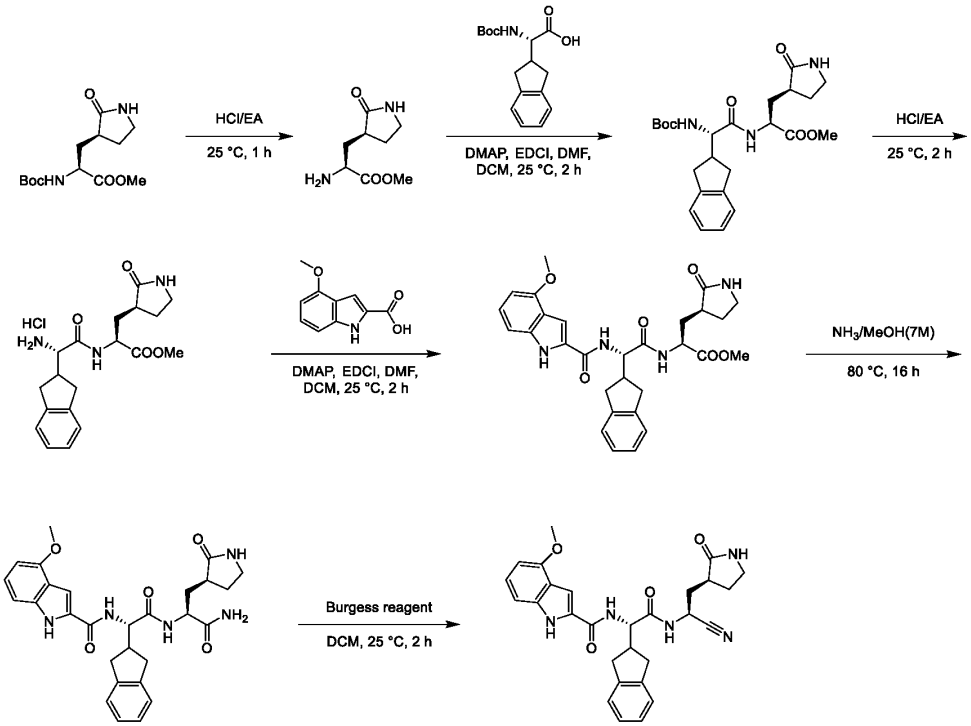
[000274] A mixture of methyl (2S)-2-[[(2S)-2-[[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (70 mg, 145.25 umol, 1 *eq*) in NH_3/MeOH (7 M, 6 mL, 97% purity, 289.17 *eq*) was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-[[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]amino]-4-methyl-pentanamide (70 mg, crude) as an oil. MS (ESI) *m/z* 467.1 $[M+H]^+$.

Step 4: (2S)-2-[[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]amino]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-pentanamide

[000275] A mixture of (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-[[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]amino]-4-methyl-pentanamide (70 mg, 149.91 umol, 1 *eq*) in DCM (1.5 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (160.77 mg, 674.62 umol, 4.5 *eq*), the mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 30%-60%, 8min) to get product (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-2-[[(E)-3-phenylprop-2-enoyl]amino]pentanamide (13.4 mg, 58.26 umol, 12.07% yield, 100% purity) as a solid. MS (ESI) *m/z* 449.1 $[M+H]^+$.

[000276] ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.67 (br d, *J*=5.7 Hz, 1H), 7.63 (d, *J*=15.7 Hz, 1H), 7.42 (t, *J*=8.3 Hz, 1H), 7.19 - 7.06 (m, 2H), 6.55 (d, *J*=15.7 Hz, 1H), 6.34 (br s, 1H), 6.19 (br s, 1H), 4.83 - 4.67 (m, 2H), 3.47 - 3.33 (m, 2H), 2.58 - 2.28 (m, 3H), 2.04 (br s, 1H), 1.95 - 1.82 (m, 1H), 1.81 - 1.62 (m, 3H), 0.99 (d, *J*=6.0 Hz, 6H)

Example 13. Synthesis of viral protease inhibitor compound 149



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000277] To a mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.75 mmol, 1 *eq*) in HCl/EtOAc (4 M, 20 mL).The mixture was stirred at 25 °C and stirred for 1 h. Once the reaction was completed, the reaction was concentrated to give the crude methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (400 mg, crude) (oil). The crude product was used directly without further purification. MS (ESI) *m/z* 187.1 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-2-indan-2-yl-acetyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000278] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (190 mg, 1.02 mmol, 1 *eq*) and (2S)-2-(tert-butoxycarbonylamino)-2-indan-2-yl-acetic acid (297.27 mg, 1.02 mmol, 1 *eq*) in DCM (9 mL) and DMF (3 mL) was added DMAP (249.31 mg, 2.04 mmol, 2 *eq*) and EDCI (391.21 mg, 2.04 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 h. Once the reaction was completed, the reaction was poured into ice-water (30 mL) and extracted with EtOAc (20 mL*3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, petroleum ether/EtOAc=1/1, 0/1) to give methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-2-indan-2-yl-acetyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 522.27 umol, 51.18% yield, 80% purity) (solid). MS (ESI) *m/z* 460.3 $[M+H]^+$

Step 3: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-2-indan-2-yl-acetyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000279] To a mixture of (S)-methyl 2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (400 mg, 870.4 umol, 1 *eq*) in HCl/EtOAc (4 M, 20 mL). The mixture was stirred at 25 °C for 2 h. Once the reaction was completed, the reaction mixture was concentrated to get the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-2-indan-2-yl-acetyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (330 mg, crude) was obtained as an oil and used directly next step. MS (ESI) *m/z* 360.2 $[M+H]^+$

Step 4: methyl (2S)-2-[[(2S)-2-amino-2-indan-2-yl-acetyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000280] To a mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-2-indan-2-yl-acetyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 652.84 umol, 1 *eq*) and 4-methoxy-1H-indole-2-carboxylic acid (149.77 mg, 783.40 umol, 1.2 *eq*) in DCM (6 mL) and DMF (2 mL) was added DMAP (159.51 mg, 1.31 mmol, 2 *eq*) and EDCI (250.30 mg, 1.31 mmol, 2 *eq*). The mixture was stirred at 25 °C and stirred for 2 h. Once the reaction was completed, the reaction was poured into ice-water (30 mL) and extracted with ethyl acetate (20 mL*3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel

chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, petroleum ether/ethyl acetate=1/1, 0/1) to give methyl (2S)-2-[[(2S)-2-amino-2-indan-2-yl-acetyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 506.96 umol, 77.66% yield, 90% purity) (solid). MS (ESI) *m/z* 533.2 $[M+H]^+$

Step 5: N-[(1S)-1-[[(1S)- 2-amino-1-[(3-methylimidazol-4-yl)methyl]-2-oxo-ethyl]carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000281] To a mixture of (S)-methyl 2-((S)-2-(2,3-dihydro-1H-inden-2-yl)-2-(4-methoxy-1H-indole-2-carboxamido)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (100 mg, 187.76 umol, 1 *eq*) was added ammonia (3.20 mg, 187.76 umol, 3.13 uL, 1 *eq*). The mixture was stirred at 80 °C and stirred for 16 h. Once the reaction was completed, the reaction was concentrated to give the crude N-((S)-2-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-(2,3-dihydro-1H-inden-2-yl)-2-oxoethyl)-4-methoxy-1H-indole-2-carboxamide (70 mg, 108.20 umol, 57.62% yield, 80% purity) as a solid. Crude product was used directly without further purification. MS (ESI) *m/z* 518.2 $[M+H]^+$

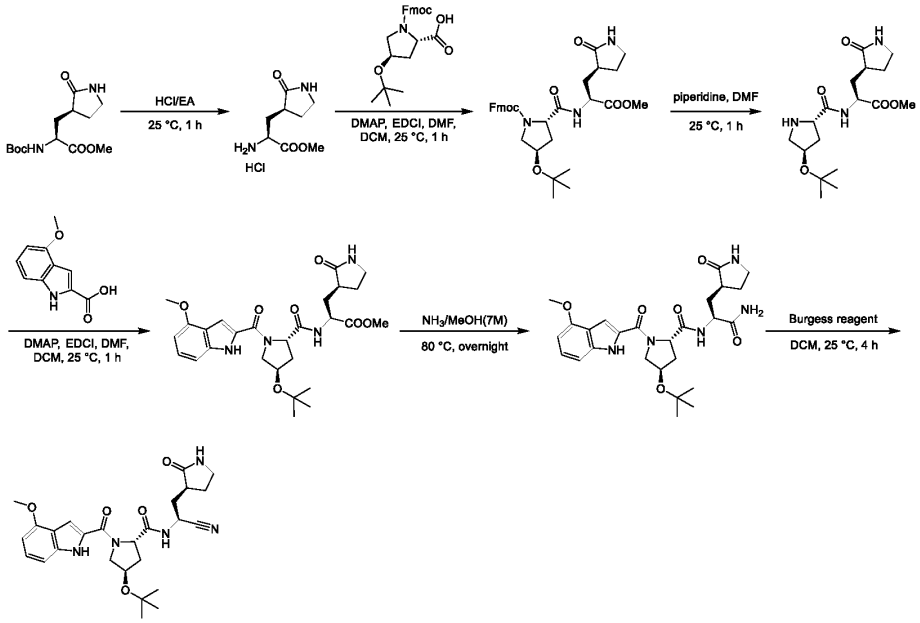
Step 6: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-indan-2-yl-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000282] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-indan-2-yl-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (60 mg, 115.93 umol, 1 *eq*) and methoxycarbonyl-(triethylammonio)sulfonyl-azanide (55.25 mg, 231.85 umol, 2 *eq*) in DCM (0.5 mL). The mixture was stirred at 25 °C and stirred for 2 h. Once the reaction was completed, the reaction was poured into ice-water (30 mL) and extracted with DCM (20 mL*3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40mm*3um; mobile phase: [water(10Mm NH_4HCO_3)-ACN];B%: 20%-50%,8min) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-indan-2-yl-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (23.83 mg, 47.70 umol, 41.15% yield, 100% purity) (solid). MS (ESI) *m/z* 500.3 $[M+H]^+$.

[000283] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.26 (s, 1 H), 7.13- 7.17 (m, 2 H), 7.11- 7.12 (m, 3 H), 7.03 (s, 1 H), 6.55– 6.52 (d, *J*=12.4 Hz, 1 H), 5.05– 5.01 (m, 1 H),

4.85- 5.00 (m, 1 H), 3.92 (s, 3 H), 3.25– 3.26 (m, 3 H), 3.21- 3.24 (m, 2 H), 2.90- 3.01 (m, 2 H), 2.88– 2.89 (m, 1 H), 2.31- 3.33 (m, 2 H), 1.81- 1.92 (m, 2 H)

Example 14. Synthesis of viral protease inhibitor compound 165



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride

[000284] Methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 873.14 umol, 1 *eq*) was added HCl/EtOAc (4 M, 30 mL) at 25 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride (200 mg, crude) as a solid and used directly for next step.

Step 2:

(2S,4R)-(9H-fluoren-9-yl)methyl-4-(tert-butoxy)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate

[000285] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (190 mg, 853.29 umol, 1 *eq*, HCl), (2S,4R)-4-tert-butoxy-1-(9H-fluoren-9-ylmethoxycarbonyl)pyrrolidine-2-carboxylic acid (349.40 mg, 853.29 umol, 1 *eq*), EDCI (327.15 mg, 1.71 mmol, 2 *eq*), DMAP (208.49 mg, 1.71 mmol, 2 *eq*), DMF (3 mL) and DCM (6 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30

mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc= 0/1) to get the product (2S,4R)-(9H-fluoren-9-yl)methyl-4-(tert-butoxy)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (230 mg, 319.96 umol, 37.50% yield, 80.36% purity), as an oil. MS (ESI) *m/z* 578.2 $[M+H]^+$

Step 3: (S)-methyl-2-((2S,4R)-4-(tert-butoxy)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000286] A mixture of (2S,4R)-(9H-fluoren-9-yl)methyl-4-(tert-butoxy)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (170 mg, 294.29 umol, 1 *eq*), piperidine (3.76 g, 8.83 mmol, 4.36 mL, 20% purity, 30 *eq*), DMF (1 mL) was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (DCM/MeOH = 10/1) to get the product (S)-methyl-2-((2S,4R)-4-(tert-butoxy)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (40 mg, 112.54 umol, 38.24% yield) as an oil.

Step 4: (S)-methyl-2-((2S,4R)-4-(tert-butoxy)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000287] A mixture of (S)-methyl-2-((2S,4R)-4-(tert-butoxy)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (40 mg, 112.54 umol, 1 *eq*), 4-methoxy-1H-indole-2-carboxylic acid (21.52 mg, 112.54 umol, 1 *eq*), EDCI (43.15 mg, 225.08 umol, 2 *eq*), DMAP (27.50 mg, 225.08 umol, 2 *eq*), DMF (0.5 mL) and DCM (1 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc= 0/1) to get the compound (S)-methyl-2-((2S,4R)-4-(tert-butoxy)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (30 mg, 22.33 umol, 19.84% yield), as an oil.

Step 5: (2S,4R)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butoxy)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

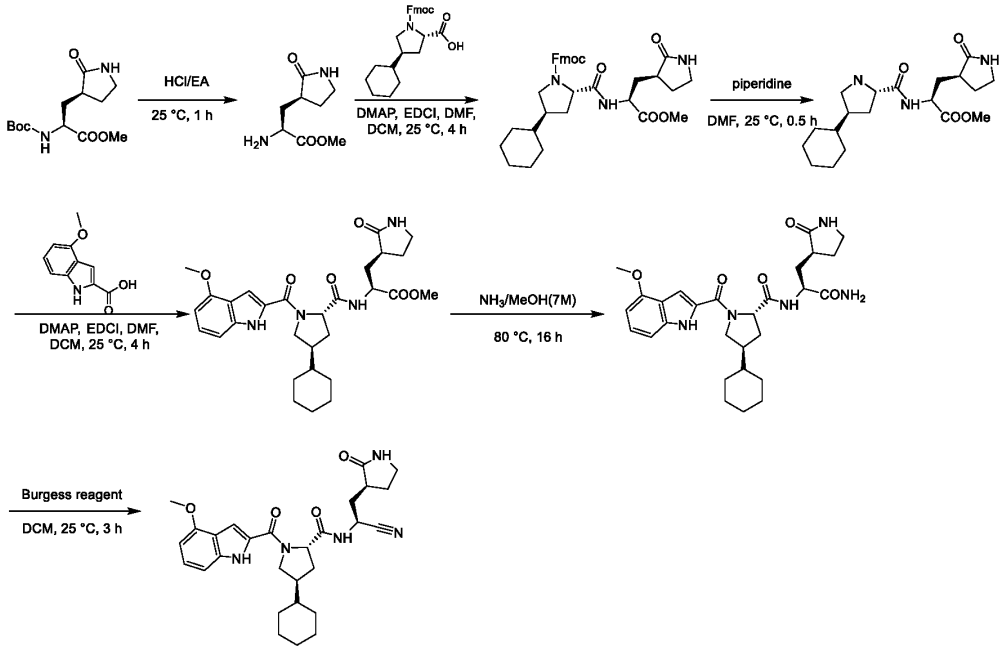
[000288] A mixture of (S)-methyl-2-((2S,4R)-4-(tert-butoxy)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (27 mg, 20.10 umol, 39.35% purity, 1 *eq*) and NH_3/MeOH (7 M, 3 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a product (2S,4R)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butoxy)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (22 mg, crude) as a solid. MS (ESI) *m/z* 514.2 $[M+H]^+$

Step 6: (2S,4R)-4-(tert-butoxy)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[000289] A mixture of (2S,4R)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butoxy)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (20 mg, 38.94 umol, 1 *eq*), Burgess reagent (27.84 mg, 116.83 umol, 3 *eq*) and DCM (1 mL) was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 20%-40%,8min) to get the product (2S,4R)-4-(tert-butoxy)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (5 mg, 10.09 umol, 25.91% yield, 100% purity), as a solid. MS (ESI) *m/z* 496.3 $[M+H]^+$.

[000290] ^1H NMR (400MHz, DMSO-d_6) δ = 11.73 - 11.43 (m, 1H), 9.26 - 8.84 (m, 1H), 7.84 - 7.49 (m, 1H), 7.19 - 7.07 (m, 1H), 7.05 - 6.96 (m, 1H), 6.94 - 6.65 (m, 1H), 6.57 - 6.41 (m, 1H), 5.08 - 4.92 (m, 1H), 4.85 - 4.40 (m, 2H), 4.34 - 4.08 (m, 1H), 3.98 - 3.75 (m, 3H), 3.74 - 3.50 (m, 1H), 3.22 - 2.80 (m, 2H), 2.47 - 2.37 (m, 1H), 2.27 - 2.04 (m, 3H), 2.03 - 1.87 (m, 1H), 1.86 - 1.36 (m, 2H), 1.15 (s, 9H)

Example 15. Synthesis of viral protease inhibitor compound 167



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000291] Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 1.05 mmol, 1 eq) in HCl/EtOAc (4 M, 5 mL, 19.09 eq) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (HCl salt, 210 mg, crude) as a solid.

Step 2: (2S,4S)-(9H-fluoren-9-yl)methyl4-cyclohexyl-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate

[000292] Methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 1.07 mmol, 1 eq) and (2*S*,4*S*)-4-cyclohexyl-1-(9*H*fluoren-9-ylmethoxycarbonyl)pyrrolidine-2-carboxylic acid (450.58 mg, 1.07 mmol, 1 eq) in DMF (1 mL) and DCM (2 mL) was added DMAP (262.43 mg, 2.15 mmol, 2 eq) and EDCI (411.80 mg, 2.15 mmol, 2 eq). The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was quenched by addition H_2O (10 mL), and then extracted with EtOAc (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 5:1 to 1:1) affording the product 9*H*-fluoren-9-ylmethyl (2*S*,4*S*)-4-cyclohexyl-2-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-

2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]pyrrolidine-1-carboxylate (500 mg, 850.77 umol, 79.21% yield) as a solid. MS (ESI) *m/z* 588.3 $[M+H]^+$

Step 3: (S)-methyl2-((2S,4S)-4-cyclohexylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000293] 9*H*-fluoren-9-ylmethyl (2*S*,4*S*)-4-cyclohexyl-2-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]pyrrolidine-1-carboxylate (480 mg, 816.74 umol, 1 eq) in DMF (4 mL) and PIPERIDINE (862.20 mg, 10.13 mmol, 1 mL, 12.40 eq) was stirred at 25 °C for 0.5 h. Upon completion, the mixture was drying with N_2 and then diluted with DCM (10 mL), concentrated under the reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) affording the product methyl (2S)-2-[[(2S,4S)-4-cyclohexylpyrrolidine-2-carbonyl]amino]-3- [(3S)-2-oxopyrrolidin-3-yl]propanoate (210 mg, 574.61 umol, 70.35% yield) as a solid.

Step 4: (S)-methyl2-((2S,4S)-4-cyclohexyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000294] Methyl(2*S*)-2-[[(2*S*,4*S*)-4-cyclohexylpyrrolidine-2-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 547.25 umol, 1 eq) and 4-methoxy-1*H*-indole-2-carboxylic acid (104.62 mg, 547.25 umol, 1 eq) in DMF (2 mL) and DCM (3 mL) was added DMAP (133.71 mg, 1.09 mmol, 2 eq) and EDCI (209.82 mg, 1.09 mmol, 2 eq). The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was quenched by addition H_2O (10 mL), and then extracted with DCM (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether:EtOAc= 0:1) affording the product methyl(2*S*)-2-[[(2*S*,4*S*)-4-cyclohexyl-1-(4-methoxy-1*H*-indole-2 -carbonyl)pyrrolidine-2-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (210 mg, 389.88 umol, 71.24% yield) as a solid. MS (ESI) *m/z* 539.2 $[M+H]^+$

Step 5: (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-cyclohexyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[000295] Methyl(2S)-2-[[(2*S*,4*S*)-4-cyclohexyl-1-(4-methoxy-*1H*-indole-2-carbonyl)pyrrolidine-2-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 371.31 umol, 1 eq) was in NH_3/MeOH (7 M, 10 mL, 188.52 eq). The mixture was

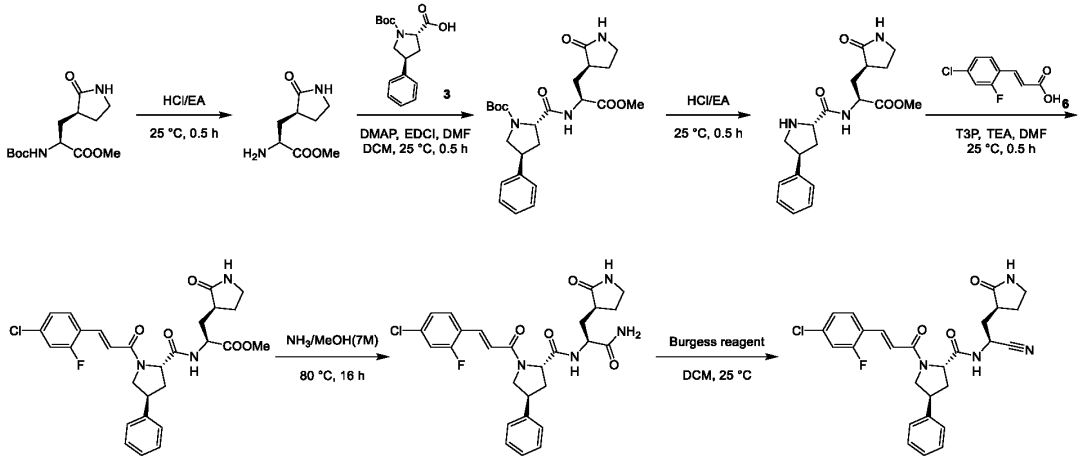
stirred at 80 °C for 16 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product (2*S*,4*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-cyclohexyl-1-(4-methoxy-1*H*indole-2-carbonyl)pyrrolidine-2-carboxamide (110 mg, crude) as a solid. MS (ESI) *m/z* 524.2 $[M+H]^+$

Step 6: (2S,4S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-4-cyclohexyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[000296] (2*S*,4*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-cyclohexyl-1-(4-methoxy-1*H*-indole-2-carbonyl)pyrrolidine-2-carboxamide (100 mg, 190.98 umol, 1 eq) in DCM (1 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (227.55 mg, 954.89 umol, 5 eq). The mixture was stirred at 25 °C for 3 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um; mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 10min) affording the product (2*S*,4*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-4-cyclohexyl-1-(4-methoxy -1*H*-indole-2-carbonyl)pyrrolidine-2-carboxamide (30.7 mg, 60.17 umol, 31.51% yield, 99.1% purity) as a solid. MS (ESI) *m/z* 506.3 $[M+H]^+$

[000297] ^1H NMR (400 MHz, MeOD-d_4) δ = 7.23 - 6.82 (m, 3H), 6.60 - 6.36 (m, 1H), 5.21 - 4.96 (m, 1H), 4.72 - 4.56 (m, 1H), 4.34 - 4.07 (m, 1H), 4.00 - 3.80 (m, 3H), 3.57 (br t, *J* = 9.4 Hz, 1H), 3.02 - 2.54 (m, 1H), 2.46 - 0.92 (m, 20H)

Example 16. Synthesis of viral protease inhibitor compound 209



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000298] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.55 g, 1.92 mmol, 1 *eq*) and HCl/EtOAc (4 M, 10 mL, 20.82 *eq*) was stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate (0.35 g, crude) as an oil.

Step 2: (2S,4S)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate

[000299] A mixture of (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate (0.15 g, 805.55 umol, 1 *eq*), (2S,4S)-1-tert-butoxycarbonyl-4-phenyl-pyrrolidine-2-carboxylic acid (234.69 mg, 805.55 umol, 1 *eq*), DMAP (196.83 mg, 1.61 mmol, 2 *eq*), EDCI (308.85 mg, 1.61 mmol, 2 *eq*) in DMF (1 mL) and DCM (2 mL) was stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 2:1 to 0:1) to give (2S,4S)-tert-butyl 2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-phenyl-pyrrolidine-1-carboxylate (0.25 g, 500.51 umol, 62.13% yield, 92% purity) as a colorless oil. MS (ESI) *m/z* 460.1 $[M+H]^+$.

Step 3: (S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-((2S,4S)-4-phenylpyrrolidine-2-carboxamido)propanoate

[000300] A mixture of tert-butyl (2S,4S)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-phenyl-pyrrolidine-1-carboxylate (0.25 g, 544.03 umol, 1 *eq*) and HCl/EtOAc (4 M, 10 mL, 73.53 *eq*) was stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(2S,4S)-4-phenylpyrrolidine-2-carbonyl]amino]propanoate (0.2 g, crude) as an oil. MS (ESI) *m/z* 360.1 $[M+H]^+$.

Step 4: (S)-methyl 2-((2S,4S)-1-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-4-phenylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000301] A mixture of methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(2S,4S)-4-phenylpyrrolidine-2-carbonyl]amino]propanoate (0.17 g, 472.99 umol, 1 *eq*), (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoic acid (94.88 mg, 472.99 umol, 1 *eq*), T3P (451.48 mg, 709.48 umol, 421.95 uL, 50% purity, 1.5 *eq*), TEA (143.58 mg, 1.42 mmol, 197.50 uL, 3 *eq*) in DMF (4 mL) was degassed stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 2:1 to 0:1) to give methyl (2S)-2-[[(2S,4S)-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.11 g, 162.36 umol, 34.33% yield, 80% purity) as a solid. MS (ESI) *m/z* 542.1 $[M+H]^+$.

Step 5: (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-4-phenylpyrrolidine-2-carboxamide

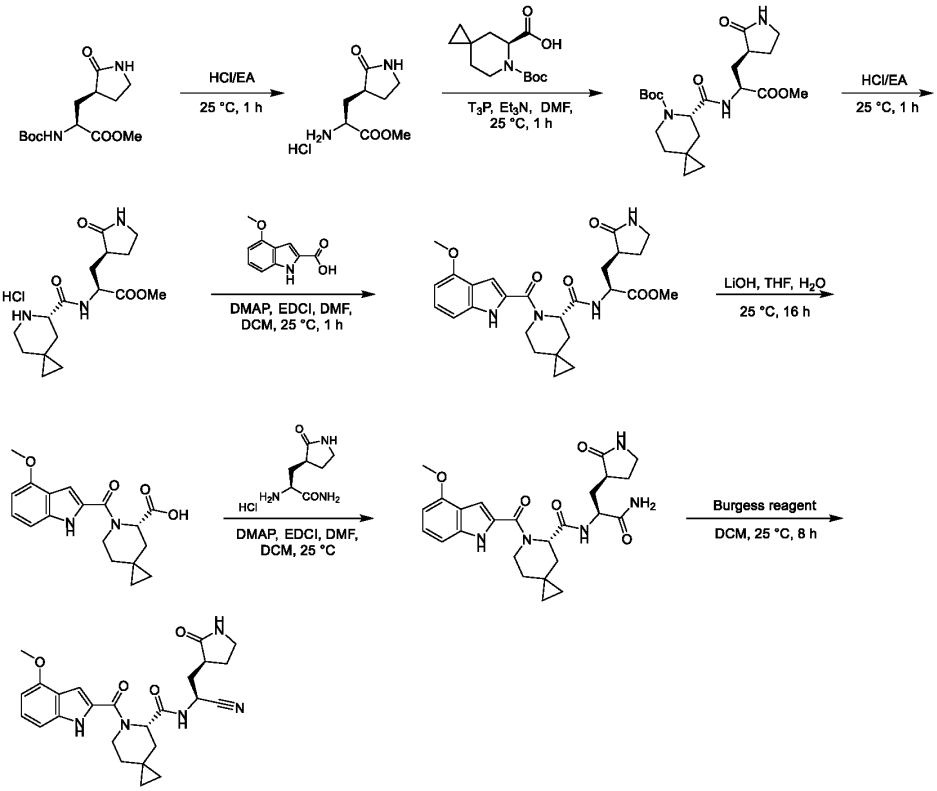
[000302] A mixture of methyl (2S)-2-[[(2S,4S)-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.1 g, 184.50 umol, 1 *eq*) in NH_3/MeOH (7M, 3 mL) was stirred at 80 °C for 16 h in the sealed tube. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-4-phenyl-pyrrolidine-2-carboxamide (0.09 g, crude) as a yellow oil. MS (ESI) *m/z* 527.0 $[M+H]^+$.

Step 6: (2S,4S)-1-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-4-phenylpyrrolidine-2-carboxamide

[000303] To a solution of (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-4-phenyl-pyrrolidine-2-carboxamide (0.09 g, 170.78 umol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (203.50 mg, 853.91 umol, 5 *eq*), the solution was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min) to give (2S,4S)-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-phenyl-pyrrolidine-2-carboxamide (29.73 mg, 56.89 umol, 33.31% yield, 97.4% purity) as a solid. MS (ESI) *m/z* 509.1 $[M+H]^+$.

[000304] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.17 - 8.86 (m, 1H), 8.07 - 7.75 (m, 1H), 7.75 - 7.65 (m, 1H), 7.62 - 7.49 (m, 2H), 7.48 - 7.30 (m, 5H), 7.26 (tt, *J* = 3.0, 5.6 Hz, 1H), 7.22 - 6.73 (m, 1H), 5.09 - 4.83 (m, 1H), 4.69 - 4.47 (m, 1H), 4.40 - 4.01 (m, 1H), 3.77 - 3.50 (m, 3H), 3.19 - 3.04 (m, 2H), 2.44 - 2.31 (m, 2H), 2.22 - 2.09 (m, 2H), 1.88 - 1.59 (m, 2H).

Example 17. Synthesis of viral protease inhibitor compound 183



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride

[000305] Methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 1.05 mmol, 1 *eq*) was added HCl/EtOAc (4 M, 30 mL) at 25 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate:HCl (230 mg, crude) as an oil and used directly for next step.

Step 2:

(S)-tert-butyl 5-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate

[000306] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (230 mg, 1.03 mmol, 1 eq, HCl), (7S)-6-tert-butoxycarbonyl-6-azaspiro[2.5]octane-7-carboxylic acid (263.72 mg, 1.03 mmol, 1 eq), T_3P (657.31 mg, 2.07 mmol, 614.31 uL, 2 eq), Et_3N (522.60 mg, 5.16 mmol, 718.85 uL, 5 eq) and DMF (5 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over

Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc= 0/1) to get the product (S)-tert-butyl 5-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (300 mg, 708.38 umol, 68.58% yield), as yellow oil. MS (ESI) *m/z* 424.1 $[M+H]^+$

Step 3: (S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-((S)-6-azaspiro[2.5]octane-5-carboxamido)propanoate

[000307] A mixture of (S)-tert-butyl 5-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (290 mg, 684.77 umol, 1 *eq*) and HCl/EtOAc (4 M, 30 mL) was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product (S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-((S)-6-azaspiro[2.5]octane-5-carboxamido)propanoate (240 mg, crude, HCl) as a an oil and used directly for next step.

Step 4: (S)-methyl 2-((S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000308] A mixture of (S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-((S)-6-azaspiro[2.5]octane-5-carboxamido)propanoate (240 mg, 666.95 umol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (127.51 mg, 666.95 umol, 1 *eq*), DMAP (162.96 mg, 1.33 mmol, 2 *eq*), EDCI (255.71 mg, 1.33 mmol, 2 *eq*), DMF (2 mL) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc= 0/1) to get the compound (S)-methyl 2-((S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (150 mg, 275.74 umol, 41.34% yield, 91.28% purity) as an oil. MS (ESI) *m/z* 495.2 $[M-H]^-$

Step 5: (S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxylic acid

[000309] A mixture of (S)-methyl 2-((S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate, LiOH (24.12 mg, 1.01 mmol, 5 *eq*), H_2O (1 mL) and THF (4 mL) was stirred at 25 °C for 16 h.

The reaction mixture was concentrated under reduced pressure to give a product (S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxylic acid (65 mg, crude) as a solid. MS (ESI) *m/z* 327.1 $[M-H]^-$

Step 6: tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate

[000310] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (400 mg, 1.40 mmol, 1 *eq*) and NH_3/MeOH (7 M, 10 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a product tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (380 mg, crude) as a solid.

Step 7: (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide

[000311] A mixture of tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (300 mg, 1.11 mmol, 1 *eq*) and HCl/EtOAc (4 M, 15 mL, 54.26 *eq*) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a product (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide (190 mg, crude) as a solid and used directly for next step.

Step 8: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxamide

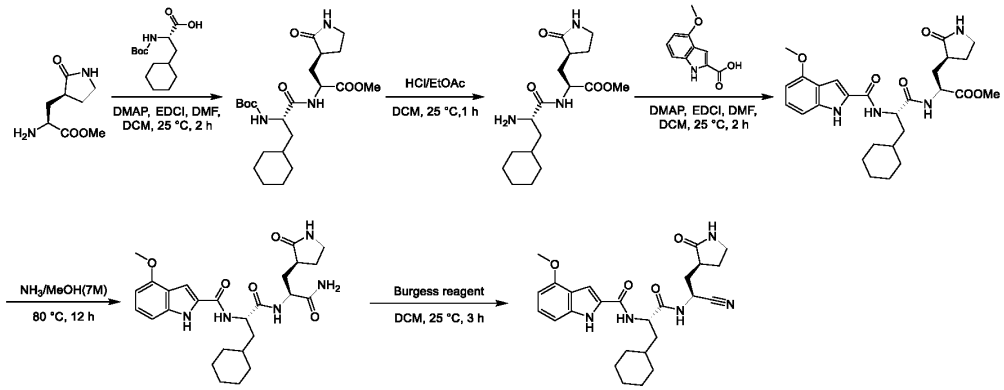
[000312] A solution of (S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxylic acid (65 mg, 197.95 umol, 1 *eq*), (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide (33.89 mg, 197.95 umol, 1 *eq*), DMAP (48.37 mg, 395.91 umol, 2 *eq*), EDCI (75.90 mg, 395.91 umol, 2 *eq*), DMF (1 mL) and DCM (3 mL) was stirred at 25 °C for 16 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 10%-40%,8min) to get the compound (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxamide (45 mg, 79.43 umol, 40.13% yield, 85% purity) as a solid. MS (ESI) *m/z* 480.2 $[M-H]^-$

Step 9: (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxamide

[000313] A mixture of (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxamide (40 mg, 83.07 umol, 1 *eq*), Burgess reagent (237.55 mg, 996.80 umol, 12 *eq*) and DCM (20 mL) was stirred at 25 °C for 8 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH_3H_2O+10mM $NH4HCO_3$)-ACN];B%: 20%-40%,8min) to get the product (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[2.5]octane-5-carboxamide (17 mg, 34.79 umol, 41.89% yield, 94.87% purity), as a solid. MS (ESI) *m/z* 462.2 $[M-H]^-$.

[000314] ^1H NMR (400MHz, DMSO-d_6) δ = 11.64 (s, 1H), 9.26 - 8.52 (m, 1H), 7.87 - 7.61 (m, 1H), 7.18 - 7.07 (m, 1H), 7.06 - 6.96 (m, 1H), 6.85 - 6.60 (m, 1H), 6.51 (d, 1H), 5.30 - 4.93 (m, 2H), 4.61 - 4.41 (m, 1H), 3.85 (s, 3H), 3.21 - 2.96 (m, 2H), 2.39 - 2.03 (m, 5H), 1.96 - 1.56 (m, 4H), 0.99 (d, 1H), 0.45 - 0.15 (m, 4H)

Example 18. Synthesis of viral protease inhibitor compound 185



Step 1: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclohexylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000315] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (170 mg, 763.47 umol, 1 eq, HCl) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-propanoic acid (207.17 mg, 763.47 umol, 1 eq) in DMF (2 mL) was added DMAP

(186.55 mg, 1.53 mmol, 2 eq) and EDCI (292.71 mg, 1.53 mmol, 2 eq). The mixture was added DCM (3 mL) and stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (30 mL) at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/EtOAc= 0/1) to get the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 568.77 umol, 74.50% yield) was obtained as a solid. MS (ESI) *m/z* 440.3 $[M+H]^+$

Step 2: (S)-methyl 2-((S)-2-amino-3-cyclohexylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000316] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclohexyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 455.02 umol, 1 eq) in EtOAc (0.5 mL) was added drop-wise HCl/EtOAc (4 M, 2.00 mL, 17.58 eq) at 25 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product methyl (2S)-2-[[(2S)-2-amino-3-cyclohexyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, crude, HCl) was obtained as a solid and used directly next step. MS (ESI) *m/z* 340.1 $[M+H]^+$

Step 3: ((S)-methyl 2-((S)-3-cyclohexyl-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000317] A solution of 4-methoxy-1H-indole-2-carboxylic acid (99.18 mg, 518.77 umol, 1.3 eq) and methyl (2S)-2-[[(2S)-2-amino-3-cyclohexyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 399.05 umol, 1 eq, HCl) in DMF (2 mL) was added DMAP (97.50 mg, 798.11 umol, 2.0 eq) and EDCI (153.00 mg, 798.11 umol, 2 eq). The mixture was added DCM (4 mL) and stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (20 mL) at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1:0 to 10:1) to get a product methyl (2S)-2-[[(2S)-3-cyclohexyl-2-[(4-methoxy-1H-indole-2-

carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 292.63 umol, 73.33% yield) was obtained as a solid.

[000318] ^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 7.26 (s, 1H), 7.09-7.20 (m, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 4.66 (br dd, J = 9.0, 6.3 Hz, 1H), 4.52-4.58 (m, 1H), 3.93 (s, 3H), 3.72 (s, 3H), 3.22-3.29 (m, 2H), 2.54-2.62 (m, 1H), 2.26-2.33 (m, 1H), 2.15-2.23 (m, 1H), 1.66-1.87 (m, 9H), 1.47-1.54 (m, 1H), 1.25-1.40 (m, 3H), 0.96-1.06 (m, 2H)

Step 4: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000319] To a solution of methyl (2S)-2-[[(2S)-3-cyclohexyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 292.63 umol, 1 eq) in ammonia (15.30 g, 898.39 mmol, 15.00 mL, 3070.07 eq) was heated to 80 °C for 12 h in a sealed tube. The reaction mixture was concentrated under reduced pressure to get a product N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclohexylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (140 mg, crude) was obtained as a solid. MS (ESI) *m/z* 498.2 $[M+H]^+$

[000320] ^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 7.27-7.34 (m, 1H), 7.13-7.20 (m, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 7.7 Hz, 1H), 4.62 (t, J = 7.6 Hz, 1H), 4.42-4.51 (m, 1H), 3.95 (s, 3H), 3.22-3.30 (m, 2H), 2.53 (td, J = 9.2, 4.5 Hz, 1H), 2.33 (ddd, J = 9.2, 6.4, 3.4 Hz, 1H), 2.17 (ddd, J = 14.1, 11.4, 4.6 Hz, 1H), 1.71-1.88 (m, 9H), 1.46-1.53 (m, 1H), 1.21-1.32 (m, 3H), 0.97-1.09 (m, 2H)

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

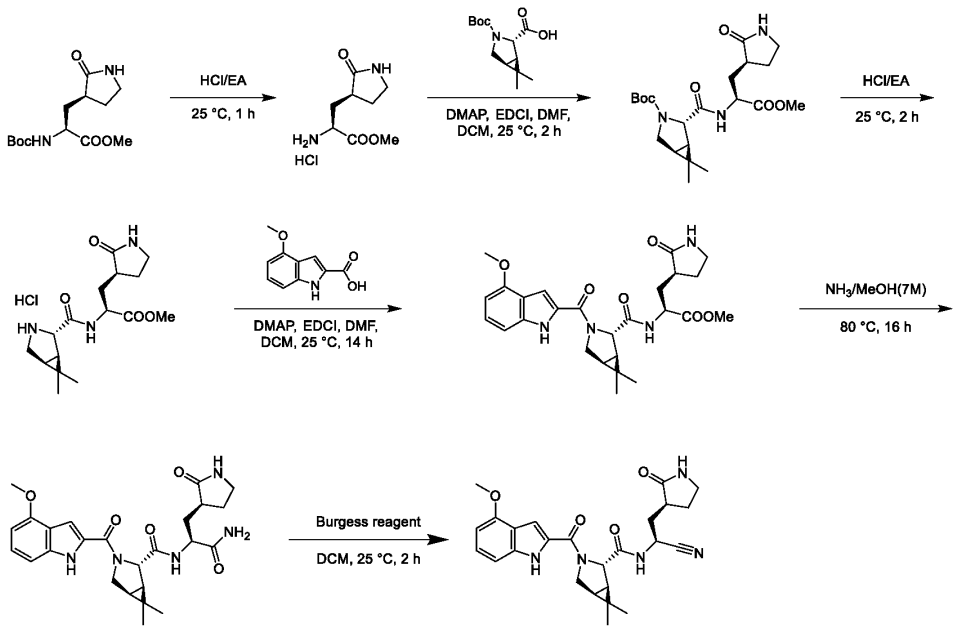
[000321] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclohexylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (80 mg, 160.78 umol, 1 eq) in DCM (3 mL) was added Burgess reagent (114.94 mg, 482.33 umol, 3 eq), then the mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC to get a product N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-

oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclohexylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (20.02 mg, 41.75 umol, 25.97% yield, 100% purity) was obtained as a solid. MS (ESI) *m/z* 480.1 $[M+H]^+$.

Prep-HPLC condition: column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min

[000322] ^1H NMR (METHANOL-d_4, 400 MHz): δ ppm 7.28 (s, 1H), 7.11-7.18 (m, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 10.1, 5.9 Hz, 1H), 4.56-4.61 (m, 1H), 3.93 (s, 3H), 3.22-3.30 (m, 2H), 2.55-2.66 (m, 1H), 2.23-2.40 (m, 2H), 1.65-1.94 (m, 9H), 1.41-1.52 (m, 1H), 1.17-1.36 (m, 3H), 0.94-1.10 (m, 2H).

Example 19. Synthesis of viral protease inhibitor compound 197



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000323] To a mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.75 mmol, 1 *eq*) in HCl/EtOAc (4M, 20 mL). The mixture was stirred at 25 °C and stirred for 1 h. Once the reaction was completed, the reaction was concentrated to give the crude methyl (2S)-2-amino-3-[(3S)-2-

oxopyrrolidin-3-yl]propanoate (400 mg, crude, an oil). The crude product was used directly without further purification. MS (ESI) *m/z* 187.1 $[M+H]^+$

Step 2: tert-butyl (2S,5S)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate

[000324] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (230 mg, 1.24 mmol, 1 *eq*) and (2S,5S)-3-tert-butoxycarbonyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (315.35 mg, 1.24 mmol, 1 *eq*) in DCM (4.5 mL) and DMF (1.5 mL) was added EDCI (473.57 mg, 2.47 mmol, 2 *eq*) and DMAP (301.80 mg, 2.47 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 h. Once the reaction was completed, the reaction was concentrated and purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-55%,10min) to give tert-butyl (2S,5S)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 425.03 umol, 34.41% yield, 90% purity) (solid). MS (ESI) *m/z* 424.1 $[M+H]^+$

Step 3: (S)-methyl 2-((1S,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000325] To a mixture of (1S,2S,5S)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 236.13 umol, 50% purity, 1 *eq*) in HCl/EtOAc (4M, 20 mL). The mixture was stirred at 25 °C and stirred for 2 h. Once the reaction was completed, the reaction was concentrated to give the crude (S)-methyl 2-((1S,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (150 mg, crude, an oil). Crude product was used directly without further purification. MS (ESI) *m/z* 324.1 $[M+H]^+$

Step 4: methyl (2S)-2-[[(2S,5S)-3-(4-methoxy-1H-indole-2-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000326] To a mixture of (S)-methyl 2-((1S,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (150 mg, 463.84 umol, 1 *eq*) and 4-methoxy-1H-indole-2-carboxylic acid (88.68 mg, 463.84 umol, 1 *eq*) in DCM (3 mL) and DMF (1 mL) was added EDCI (177.84 mg, 927.68 umol,

2 *eq*) and DMAP (113.33 mg, 927.68 umol, 2 *eq*). The mixture was stirred at 25 °C and stirred for 14 h. Once the reaction was completed, the mixture was poured into water (50 mL) and extracted with DCM (20 mL*3).The combined organic phase was washed with brine (60 mL*3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, petroleum ether/ethyl acetate=1/1, 0/1) to afford methyl (2S)-2-[[(2S,5S)-3-(4-methoxy-1H-indole-2-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (50 mg, 80.56 umol, 17.37% yield, 80% purity) as solid. MS (ESI) *m/z* 497.2 $[M+H]^+$

Step 5: (2S,5S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

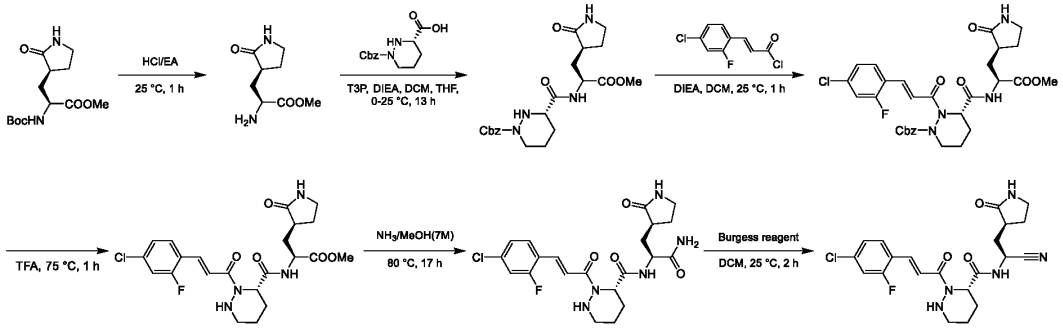
[000327] To a mixture of methyl (2S)-2-[[(2S,5S)-3-(4-methoxy-1H-indole-2-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (100 mg, 201.39 umol, 1 *eq*) in ammonia (5.10 g, 299.46 mmol, 5 mL, 1486.99 *eq*). The mixture was stirred at 80 °C and stirred for 16 h. Once the reaction was completed, the reaction was concentrated to give the crude (2S,5S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (100 mg, crude) (solid). Crude product was used directly without further purification. MS (ESI) *m/z* 482.3$[M+H]^+$

Step 6: (2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

[000328] To a mixture of (2S,5S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (50 mg, 103.83 umol, 1 eq) in DCM (3 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (49.49 mg, 207.67 umol, 2 eq). The mixture was stirred at 25 °C for 2 h. Once the reaction was completed, the reaction was concentrated and purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40mm*3um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 20%-40%,8min) to give (2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (14.44 mg, 31.15 umol, 30.00% yield, 100% purity) as a solid. MS (ESI) m/z 464.2[M+H]+.

[000329] 1H NMR (400 MHz, METHANOL-d4): δ ppm 7.16 - 7.18 (m, 1 H), 7.11- 7.14 (m, 2 H), 6.4 – 6.88 (m, 1 H), 5.05- 5.08 (m, 0.5 H), 4.06 (s, 2 H), 3.94- 3.98 (m, 0.5 H), 3.77 – 3.86 (m, 4 H), 3.28 (s, 2 H), 2.61- 3.69 (m, 1 H), 2.27- 2.32 (m, 1 H), 2.25- 2.26 (m, 1 H), 1.78 – 2.00 (m, 1 H), 1.74- 1.75 (m, 1 H) 1.35– 1.64 (m, 2 H), 0.97- 1.15 (m, 6 H)

Example 20. Synthesis of viral protease inhibitor compound 213



Step 1: (S)-Methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000330] Methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (501 mg, 1.75 mmol, 1 eq) in HCl/EtOAc (4 M, 10.02 mL, 22.91 eq) was stirred at 25 °C for 1 h. Upon completion, the solution was concentrated. The crude was used to next step directly and without further purification. Methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl] propanoate (300 mg, crude) was obtained as yellow oil.

Step 2: (S)-benzyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)tetrahydropyridazine-1(2H)-carboxylate

[000331] Methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (295.93 mg, 1.59 mmol, 1.4 eq) and (3S)-1-benzyloxycarbonylhexahydropyridazine-3-carboxylic acid (300 mg, 1.14 mmol, 1 eq) in DCM (2 mL)/THF (2 mL) was cooled to 0 °C, then the T3P (1.08 g, 1.70 mmol, 1.01 mL, 50% purity, 1.5 eq) and DIEA (440.14 mg, 3.41 mmol, 593.18 uL, 3 eq) was added and the solution was stirred at 25 °C for 13 h. Upon completion, the solution was diluted with H_2O (20 mL), extracted with Ethyl acetate (30 mL*3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The crude was used to next step directly and without further purification. Benzyl (3S)-3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl] ethyl]

carbamoyl] hexahydropyridazine-1-carboxylate (455 mg, crude) was obtained as yellow oil. MS (ESI) *m/z* 433.1 $[M+H]^+$.

Step 3: (S)-benzyl 2-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)tetrahydropyridazine-1(2H)-carboxylate

[000332] Benzyl (3S)-3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]hexahydropyridazine-1-carboxylate (200 mg, 462.46 umol, 1 eq) in DCM (2 mL) was added the DIEA (119.54 mg, 924.92 umol, 161.10 uL, 2 eq), (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl chloride (121.56 mg, 554.95 umol, 1.2 eq) was added and the solution was stirred at 25 °C for 1 h. Upon completion, the solution was diluted with H_2O (10 mL), extracted with DCM (20 mL*3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1). Benzyl (3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl) prop-2-enoyl]-3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl] ethyl] carbamoyl] hexahydropyridazine-1-carboxylate (160 mg, 248.88 umol, 53.82% yield, 95.67% purity) was obtained as yellow oil. MS (ESI) *m/z* 433.1 $[M+H]^+$.

Step 4: (S)-methyl 2-((S)-2-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)hexahydropyridazine-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000333] Benzyl (3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]hexahydropyridazine-1-carboxylate (160 mg, 260.14 umol, 1 eq) in TFA (5 mL) was stirred at 75 °C for 1 h. Upon completion, the solution was concentrated to remove the TFA, diluted with the solution of $NaHCO_3$, extracted with EtOAc (20 mL*3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The crude was used to next step directly and without further purification. Methyl (2S)-2-[[(3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl) prop-2-enoyl] hexahydropyridazine-3-carbonyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propanoate (80 mg, crude) was obtained as solid. MS (ESI) *m/z* 481.0 $[M+H]^+$.

Step 5: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)hexahydropyridazine-3-carboxamide

[000334] Methyl (2S)-2-[[(3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]hexahydropyridazine-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (80 mg, 166.35 umol, 1 eq) in NH_3/MeOH (7 M, 4.00 mL, 168.32 eq) was stirred at 80 °C for 17 h. Upon completion, the solution was concentrated to remove the MeOH. The crude was used to next step directly and without further purification. (3S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl] ethyl]-2-[(E)-3-(4-chloro-2-fluoro-phenyl) prop-2-enoyl] hexahydropyridazine-3-carboxamide (75 mg, crude) was obtained as yellow oil. MS (ESI) *m/z* 481.0 $[M+H]^+$.

Step 6: (S)-2-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)hexahydropyridazine-3-carboxamide

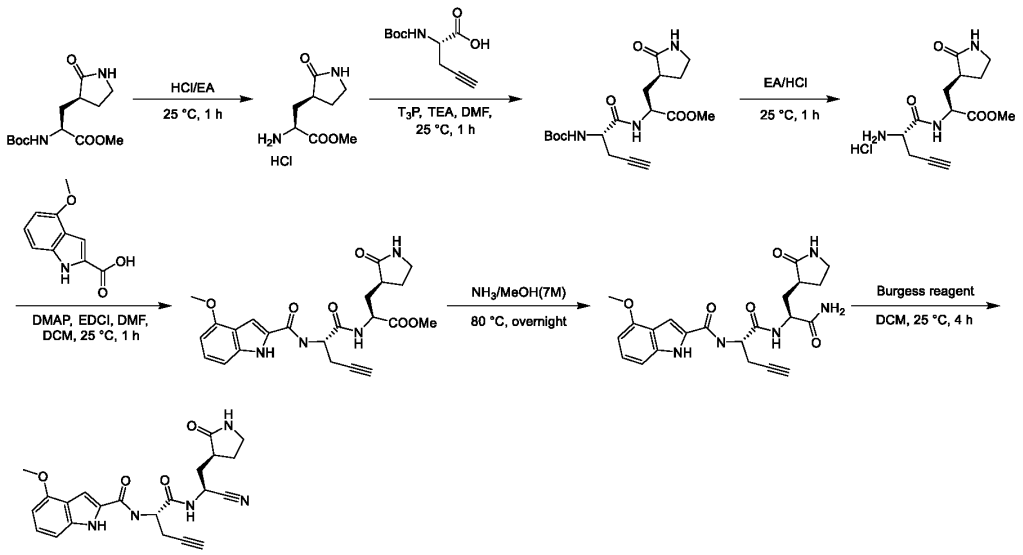
[000335] (3S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]hexahydropyridazine-3-carboxamide (75 mg, 160.98 umol, 1 eq) in DCM (0.5 mL) was added the Burgess reagent (76.72 mg, 321.95 umol, 2 eq) and the solution was stirred at 25 °C for 2 h. Upon completion, the solution was concentrated to remove the DCM. The residue was purified by prep-HPLC (neutral condition). Column: Phenomenex Gemini-NX 80*40mm*3um; mobile phase: [water (10mM NH4HCO3)-ACN]; B%: 25%-45%, 8min. (3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]hexahydropyridazine-3-carboxamide (20 mg, 44.65 umol, 27.74% yield, 100% purity) was obtained as a solid. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.79 - 7.60 (m, 3H), 7.32 - 7.22 (m, 2H), 5.17 (dd, *J*=2.2, 6.0 Hz, 1H), 5.07 (dd, *J*=6.4, 9.7 Hz, 1H), 3.38 - 3.32 (m, 2H), 3.12 (br d, *J*=13.7 Hz, 1H), 2.90 - 2.74 (m, 1H), 2.56 (dq, *J*=5.8, 9.0 Hz, 1H), 2.44 - 2.14 (m, 3H), 2.08 - 1.79 (m, 3H), 1.75 - 1.53 (m, 2H). MS (ESI) *m/z* 448.2 $[M+H]^+$.

Step 7: (E)-3-(4-chloro-2-fluorophenyl)acryloyl chloride

[000336] (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoic acid (120 mg, 598.22 umol, 1 eq) in DCM (0.5 mL) was added the DMF (437.26 ug, 5.98 umol, 0.46 uL, 0.01 eq) and cooled to 0 °C, then the $(COCl)_2$ (151.86 mg, 1.20 mmol, 104.73 uL, 2 eq) was added and the solution was stirred at 25 °C for 1 h. Upon completion, the solution was concentrated to remove the DCM and give the crude. The crude was used to next step directly and

without further purification. (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl chloride (125 mg, crude) was obtained as a solid.

Example 21. Synthesis of viral protease inhibitor compound 201



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride

[000337] Methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 873.14 umol, 1 *eq*) was added HCl/EtOAc (4 M, 30 mL) at 25 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride (200 mg, crude) as a solid and used directly for next step.

Step 2: (S)-methyl-2-((S)-2-((tert-butoxycarbonyl)amino)pent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000338] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride (180 mg, 808.38 umol, 1 *eq*), (2S)-2-(tert-butoxycarbonylamino)pent-4-ynoic acid (172.37 mg, 808.38 umol, 1 *eq*), TEA (572.59 mg, 5.66 mmol, 787.61 uL, 7 *eq*), T_3P (1.03 g, 1.62 mmol, 961.53 uL, 50% purity, 2 *eq*) and DMF (3 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure

to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc= 0/1) to afford the product (S)-methyl-2-((S)-2-((tert-butoxycarbonyl)amino)pent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (150 mg, 393.26 umol, 48.65% yield), as an oil. MS (ESI) *m/z* 382.1 $[M+H]^+$

Step 3: (S)-methyl 2-((S)-2-aminopent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000339] A mixture of (S)-methyl-2-((S)-2-((tert-butoxycarbonyl)amino)pent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (140 mg, 367.05 umol, 1 *eq*) and HCl/EtOAc (4 M, 30 mL) was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product (S)-methyl 2-((S)-2-aminopent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (120 mg, crude, HCl) as an oil and used directly for next step.

Step 4: (S)-methyl-2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)pent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000340] A mixture of (S)-methyl 2-((S)-2-aminopent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (120 mg, 377.63 umol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (72.20 mg, 377.63 umol, 1 *eq*), EDCI (144.78 mg, 755.27 umol, 2 *eq*), DMAP (92.27 mg, 755.27 umol, 2 *eq*), DMF (2 mL) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc= 0/1) to get the compound (S)-methyl-2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)pent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (90 mg, 160.56 umol, 42.52% yield, 81.08% purity), as an oil. MS (ESI) *m/z* 455.1 $[M+H]^+$

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopent-4-yn-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000341] A mixture of (S)-methyl-2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)pent-4-ynamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (85 mg, 187.03 umol, 1 *eq*) and NH_3/MeOH (7 M, 10 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a product N-((S)-1-(((S)-1-amino-1-oxo-3-

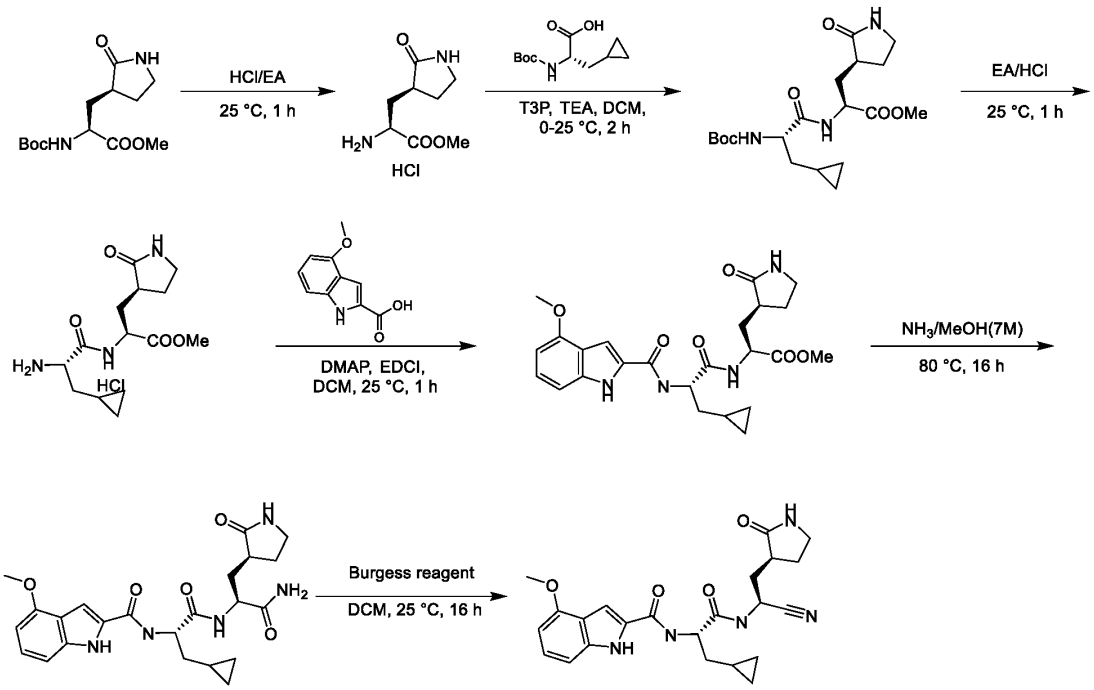
((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopent-4-yn-2-yl)-4-methoxy-1H-indole-2-carboxamide (85 mg, crude) as a solid. MS (ESI) *m/z* 440.2 $[M+H]^+$

Step 6: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-1-oxopent-4-yn-2-yl)-4-methoxy-1H-indole-2-carboxamide

[00342] A mixture of N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopent-4-yn-2-yl)-4-methoxy-1H-indole-2-carboxamide (80 mg, 182.04 umol, 1 *eq*), Burgess reagent (216.91 mg, 910.20 umol, 5 *eq*) and DCM (5 mL) was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(0.04%NH_3H_2O+10mM $NH4HCO_3$)-ACN];B%: 20%-50%,10min) to get the product N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-1-oxopent-4-yn-2-yl)-4-methoxy-1H-indole-2-carboxamide (20 mg, 47.46 umol, 26.07% yield, 100% purity), as solid. MS (ESI) *m/z* 422.2 $[M+H]^+$.

[00343] ^1H NMR (400MHz, DMSO-d_6) δ = 11.61 (d, J=1.8 Hz, 1H), 9.18 - 8.93 (m, 1H), 8.74 - 8.58 (m, 1H), 7.78 - 7.62 (m, 1H), 7.37 - 7.29 (m, 1H), 7.15 - 7.07 (m, 1H), 7.05 - 6.97 (m, 1H), 6.51 (d, J=7.5 Hz, 1H), 5.03 - 4.91 (m, 1H), 4.65 - 4.50 (m, 1H), 3.89 (s, 3H), 3.20 - 3.05 (m, 2H), 2.91-2.85 (m, 1H), 2.78 - 2.59 (m, 2H), 2.43 - 2.29 (m, 1H), 2.21 - 2.06 (m, 2H), 1.88 - 1.59 (m, 2H)

Example 22. Synthesis of viral protease inhibitor compound 205



Step 1: (S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpropanoic acid

[00344] To a solution of (2*S*)-2-amino-3-cyclopropyl-propanoic acid (1 g, 7.74 mmol, 1 *eq*) in THF (5 mL) and H_2O (5 mL), was added K_2CO_3 (3.75 g, 27.10 mmol, 3.5 *eq*) and $(Boc)_2O$ (2.20 g, 10.07 mmol, 2.31 mL, 1.3 *eq*). Additional water was added to the mixture, and then the mixture was stirred at 25 °C for 16 h. The organic solvent was then evaporated and the aqueous solution was washed with petroleum ether (10 mL) and acidified to pH ~3 with 1N aqueous citric acid (30 mL). The solution was extracted with DCM (30 mL * 3) and was concentrated in vacuum to afford (*S*)-2-((*tert*-butoxycarbonyl) amino)-3-cyclopropyl propanoic acid (1.8 g, crude) as an oil.

Step 2: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[00345] (*S*)-methyl 2-((*tert*-butoxycarbonyl) amino)-3-((*S*)-2-oxopyrrolidin-3-yl) propanoate (500 mg, 1.75 mmol, 1 *eq*) was added HCl/EtOAc (4 M, 5 mL) at 25 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product (*S*)-methyl 2-amino-3-((*S*)-2-oxopyrrolidin-3-yl) propanoate (350 mg, HCl, crude) as a yellow gum and used to next step directly.

Step 3: (S)-methyl2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000346] To a mixture of (*S*)-methyl 2-amino-3-((*S*)-2-oxopyrrolidin-3-yl) propanoate (250 mg, 1.12 mmol, 1 *eq*, HCl) and (*S*)-2-((*tert*-butoxycarbonyl) amino)-3-cyclopropyl propanoic acid (386.12 mg, 1.68 mmol, 1.5 *eq*) in DCM (5 mL) was added TEA (568.05 mg, 5.61 mmol, 781.36 uL, 5 *eq*) at 0°C, the mixture was added T3P (2.14 g, 3.37 mmol, 2.00 mL, 50% purity, 3 *eq*) at 0°C, then the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by water (10 mL) and was extracted with DCM (5 mL * 3). The resulting solution was dried with Na_2SO_4, filtered and concentration in vacuum to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:EtOAc= 1:0 to 0:1) to afford the product (*S*)-methyl 2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (400 mg, 905.74 umol, 80.67% yield, 90% purity) was obtained as a gum.

[000347] ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.60 (d, *J* = 5.6 Hz, 1H), 5.96 (s, 1H), 5.24 (d, *J* = 7.5 Hz, 1H), 4.65 - 4.47 (m, 1H), 4.24 (d, *J* = 6.6 Hz, 1H), 3.73 (s, 3H), 3.44 - 3.27 (m, 2H), 2.51 - 2.36 (m, 2H), 2.25 - 2.13 (m, 1H), 1.98 - 1.82 (m, 1H), 1.66 - 1.58 (m, 1H), 1.44 (s, 9H), 1.30 - 1.21 (m, 1H), 0.86 - 0.71 (m, 1H), 0.49 (d, *J* = 7.9 Hz, 2H), 0.13 (d, *J* = 4.4 Hz, 2H).

Step 4: (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000348] A solution of (*S*)-methyl2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-cyclopropylpropanamido)-3- ((*S*)-2- oxopyrrolidin-3-yl)propanoate in HCl/EtOAc (4 M, 4 mL), the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product (*S*)-methyl 2-((*S*)-2-amino-3-cyclopropylpropanamido)-3-((*S*)-2-oxopyrrolidin-3-yl) propanoate (330 mg, crude, HCl) as a yellow gum and used directly next step.

[000349] 1H NMR (400 MHz, MeOD-d_4) δ ppm 4.57 (dd, *J* = 4.1, 11.0 Hz, 1H), 3.94 (t, *J* = 6.7 Hz, 1H), 3.73 (s, 3H), 3.40 - 3.33 (m, 2H), 2.55 - 2.33 (m, 2H), 2.19 - 2.07 (m, 1H), 2.03 - 2.00 (m, 1H), 1.93 - 1.84 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 1H), 0.89 - 0.79 (m, 1H), 0.59 (dd, *J* = 4.5, 7.9 Hz, 2H), 0.26 - 0.17 (m, 2H).

Step 5: (S)-methyl2-((S)-3-cyclopropyl-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000350] To a mixture of 4-methoxy-1*H*-indole-2-carboxylic acid (257.73 mg, 1.35 mmol, 1.5 *eq*) and (*S*)-methyl 2-((*S*)-2-amino-3-cyclopropylpropanamido)-3-((*S*)-2-oxopyrrolidin-3-yl) propanoate (300 mg, 898.71 umol, 1 *eq*, HCl) in DCM (8 mL) was added EDCI (861.43 mg, 4.49 mmol, 5 *eq*) and DMAP (329.38 mg, 2.70 mmol, 3 *eq*), then the mixture was stirred at 25 °C for 2 h. The combined organic layers were quenched with water (10 mL) and were extracted with DCM (4 mL * 3). The resulting solution was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, EtOAc) to get the compound (*S*)-methyl2-((*S*)-3-cyclopropyl-2-(4-methoxy-1*H*-indole-2-carboxamido)propanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (250 mg, 425.06 umol, 47.30% yield, 80% purity) as yellow oil. MS (ESI) *m/z* 471.1 $[M+H]^+$

Step 6: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000351] (*S*)-Methyl2-((*S*)-3-cyclopropyl-2-(4-methoxy-1*H*-indole-2-carboxamido)propanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (250 mg, 531.33 umol, 1 *eq*) was added with NH_3/MeOH (7 M, 6.00 mL). The mixture was stirred at 80 °C for 16 h. The resulting mixture was concentrated under reduced pressure to give a residue *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl) amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (200 mg, crude) as a solid. MS (ESI) *m/z* 456.1 $[M+H]^+$

Step 7: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

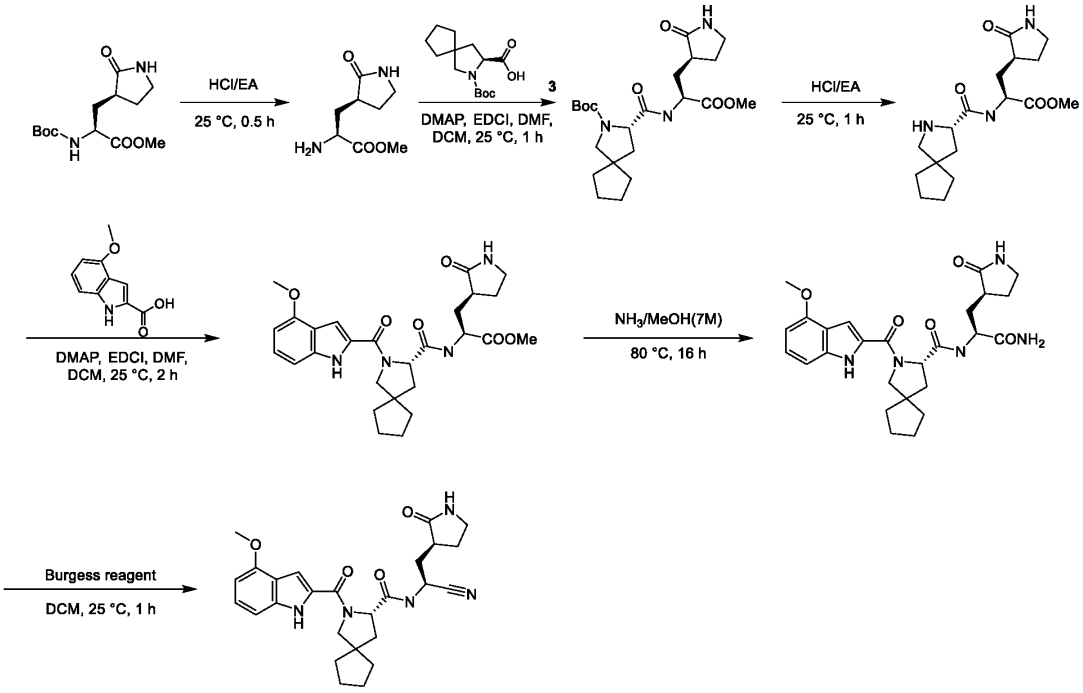
[000352] To a mixture of *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl) amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (100 mg, crude) in DCM (4 mL) was added Burgess reagent (104.63 mg, 439.07 umol, 2 *eq*). The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched by water (0.5 mL) and was dried by blowing N_2. The residue was purified by neutral prep-HPLC to get the product *N*-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (15 mg, 34.29 umol, 15.62% yield, 100% purity) as a solid. MS (ESI) *m/z* 438.2 $[M+H]^+$.

prep-HPLC condition:

column: Waters Xbridge BEH C18 100 * 25mm * 5 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 20%-50%, 10 min .

[000353] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.57 (d, J = 1.8 Hz, 1H), 8.90 (d, J = 8.2 Hz, 1H), 8.50 (d, J = 7.5 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.36 (d, J = 1.5 Hz, 1H), 7.13 - 7.04 (m, 1H), 7.03 - 6.96 (m, 1H), 6.50 (d, J = 7.8 Hz, 1H), 5.04 - 4.94 (m, 1H), 4.54 - 4.38 (m, 1H), 3.89 (s, 3H), 3.19 - 3.06 (m, 2H), 2.44 - 2.33 (m, 1H), 2.22 - 2.07 (m, 2H), 1.90 - 1.75 (m, 2H), 1.74 - 1.63 (m, 1H), 1.54 - 1.41 (m, 1H), 0.87 - 0.73 (m, 1H), 0.47 - 0.34 (m, 2H), 0.25 - 0.15 (m, 1H), 0.14 - 0.04 (m, 1H).

Example 23. Synthesis of viral protease inhibitor compound 401



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000354] Methyl (2*S*)-2-(tert-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (400 mg, 1.40 mmol, 1 eq) in HCl/EtOAc (4 M, 10 mL, 28.63 eq) was stirred at 25 °C for 0.5 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (300 mg, crude, HCl) as a solid.

Step 2: (S)-tert-butyl3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.4]nonane-2-carboxylate

[000355] Methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 1.35 mmol, 1 eq, HCl) and (3*S*)-2-tertbutoxycarbonyl-2-azaspiro[4.4]nonane-3-carboxylic acid (362.87 mg, 1.35 mmol, 1 eq) in DMF (2 mL) and DCM (5 mL) was added DMAP (329.19 mg, 2.69 mmol, 2 eq) and EDCI (516.56 mg, 2.69 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (10 mL), and then extracted with DCM (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 5:1 to 0:1) affording the product *tert*-butyl(3*S*)-3-[[(1*S*)-2-methoxy-2-oxo-1- [[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.4]nonane-2-carboxylate (340 mg, 777.09 umol, 57.68% yield) as an oil.

Step 3: (S)-methyl3-((S)-2-oxopyrrolidin-3-yl)-2-((S)-2-azaspiro[4.4]nonane-3-carboxamido)propanoate

[000356] *tert*-Butyl(3*S*)-3-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.4]nonane-2-carboxylate (340 mg, 777.09 umol, 1 eq) in HCl/EtOAc (4 M, 10 mL, 51.47 eq) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressured affording the product methyl(2*S*)-2-[[(3*S*)-2-azaspiro[4.4]nonane-3-carbonyl]amino] -3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (250 mg, crude, HCl) as an oil.

Step 4: (S)-methyl2-((S)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000357] Methyl(2*S*)-2-[[(3*S*)-2-azaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 668.67 umol, 1 eq, HCl) and 4-methoxy-1*H*-indole-2-carboxylic acid (127.84 mg, 668.67 umol, 1 eq) in DMF (2 mL) and DCM (6 mL) was added DMAP (163.38 mg, 1.34 mmol, 2 eq) and EDCI (256.37 mg, 1.34 mmol, 2 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (10 mL), and then extracted with DCM (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by

prep-TLC (SiO_2, petroleum ether:EtOAc= 0:1) affording the product methyl(2*S*)-2-[[(3*S*)-2-(4-methoxy-1*H*-indole-2-carbonyl)-2 -azaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (180 mg, 352.54 umol, 52.72% yield) as an oil. MS (ESI) *m/z* 511.2 $[M+H]^+$

Step 5: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide

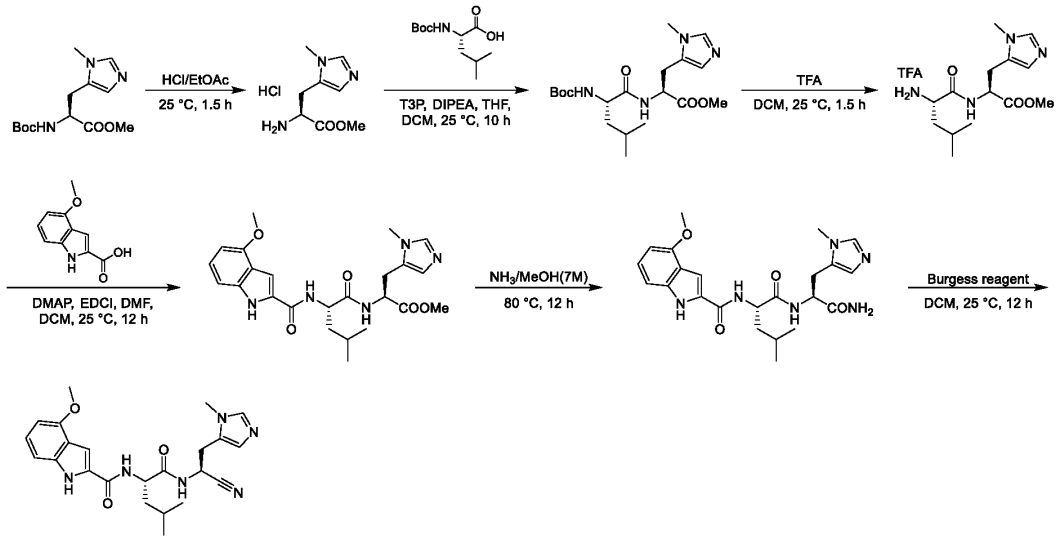
[000358] Methyl(2*S*)-2-[[(3*S*)-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (180 mg, 352.54 umol, 1 eq) in ammonia (7 M, 20 mL, 397.12 eq) was stirred at 80 °C for 16 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product (3*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl] methyl]ethyl]-2-(4-methoxy-1*H*-indole-2- carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (170 mg, crude) as an oil.

Step 6: (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide

[000359] (3*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (170 mg, 343.04 umol, 1 eq) in DCM (3 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (408.74 mg, 1.72 mmol, 5 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 10 min) affording the product (3*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2 -carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (25 mg, 51.09 umol, 14.89% yield, 97.6% purity) as a solid. MS (ESI) *m/z* 478.2 $[M+H]^+$

[000360] ^1H NMR (400 MHz, MMeOD-d_4) δ = 7.22 - 7.12 (m, 1H), 7.11 - 6.98 (m, 2H), 6.58 - 6.45 (m, 1H), 5.11 - 4.95 (m, 1H), 4.65 - 4.52 (m, 1H), 3.94 (s, 3H), 3.93 - 3.80 (m, 2H), 3.28 - 3.18 (m, 1H), 2.54 - 2.02 (m, 4H), 2.01 - 1.48 (m, 12 H).

Example 24. Synthesis of viral protease inhibitor compound 225



Step 1: methyl (2S)-2-amino-3-(3-methylimidazol-4-yl)propanoate

[000361] To the solution of (2S)-2-(tert-butoxycarbonylamino)-3-(3-methylimidazol-4-yl)propanoic acid (300 mg, 1.11 mmol, 1 *eq*) in EtOAc (1.2 mL) was added HCl/EtOAc (4 M, 2.79 mL, 10 *eq*) at 25 °C. The reaction mixture was stirred at 25 °C for 1.5 h. The resulting mixture was concentrated to get the product. Methyl (2S)-2-amino-3-(3-methylimidazol-4-yl)propanoate (250 mg, crude, HCl) was obtained as a solid and used directly next step. MS (ESI) *m/z* 183.2 $[M+H]^+$

[000362] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.94 (s, 1 H), 7.56 (s, 1 H), 4.51 (t, *J*=7.17 Hz, 1 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.46 - 3.55 (m, 1 H), 3.32 - 3.42 (m, 1 H).

Step 2: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-(3-methyli midazol-4-yl)propanoate

[000363] To a mixture of methyl (2S)-2-amino-3-(3-methylimidazol-4-yl)propanoate (250 mg, 1.14 mmol, 1 *eq*, HCl) and (2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoic acid (263.22 mg, 1.14 mmol, 1 *eq*) in THF (1 mL) and DCM (1 mL) and DIPEA (441.26 mg, 3.41 mmol, 594.69 uL, 3 *eq*) was added T3P (1.09 g, 1.71 mmol, 1.02 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 10 h. LCMS showed the reaction mixture was completed. The reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL x 2) to get the organic phase. The organic phase was washed with brine (3 mL x 3), dried over anhydrous sodium sulfate and concentrated to get the crude product. Methyl (2S)-2-

[[(2S)-2-(tert-butoxy carbonyl amino)-4-methyl-pentanoyl]amino]-3-(3-methylimidazol-4-yl)propanoate (360 mg, crude) was obtained as an oil and used directly next step. MS (ESI) *m/z* 397.3 $[M+H]^+$

Step 3: methyl(2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-(3-methylimidazol-4-yl)propanoate

[000364] To a mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]- 3-(3-methylimidazol-4-yl)propanoate (360 mg, 907.99 umol, 1 *eq*) in DCM (3.3 mL) was added TFA (1.04 g, 9.08 mmol, 672.27 uL, 10 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 1.5 h. LCMS showed the reaction mixture was completed. The reaction mixture was concentrated to get the product. Methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-(3-methylimidazol-4-yl) propanoate (370 mg, crude, TFA) was obtained as an oil and used directly next step. MS (ESI) *m/z* 297.2 $[M+H]^+$

Step 4: methyl (2S)-2-[[(2S)-2-[(4-methoxy- 1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino] -3-(3-methylimidazol-4-yl)propanoate

[000365] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-(3-methylimidazol-4- yl)propanoate (370 mg, 1.25 mmol, 1 *eq*, TFA) and 4-methoxy-1H-indole-2-carboxylic acid (238.69 mg, 1.25 mmol, 1 *eq*) in DMF (1.5 mL) and DCM (1.5 mL) was added EDCI (478.66 mg, 2.50 mmol, 2 *eq*) and DMAP (305.05 mg, 2.50 mmol, 2 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The resulting mixture was added with water (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was washed with brine (3 mL * 3) and dried over anhydrous sodium sulfate and concentrated to get the crude product. The residue was purified by column chromatography (SiO2, petroleum ether/EtOAc=2/1 to EtOAc/Methanol = 10/1). Methyl (2S)-2-[[(2S)-2-[(4-methoxy- 1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-(3-methylimidazol-4-yl)propanoate (270 mg, crude) was obtained as an oil. MS (ESI) *m/z* 469.5 $[M+H]^+$

Step 5: N-[(1S)-1-[[(1S)- 2-amino-1-[(3-methylimidazol-4-yl)methyl]-2-oxo-ethyl]carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000366] To methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]- 3-(3-methylimidazol-4-yl)propanoate (235.00 mg, 500.50 umol, 1 *eq*)

was added NH_3/MeOH (7 M, 1.94 mL, 27.14 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C and stirred for 12 h. LCMS showed the reaction mixture was completed. The reaction mixture was cooled to 25°C and concentrated to get the crude product. The residue was purified by prep-TLC. N-[(1S)-1-[[(1S)- 2-amino-1-[(3-methylimidazol-4-yl)methyl]-2-oxo-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (170 mg, crude) was obtained as a solid. MS (ESI) *m/z* 455.3 $[M+H]^+$

Step 6: N-[(1S)-1-[[(1S)-1-cyano-2-(3-methylimidazol-4-yl)ethyl]carbamoyl]-3-methyl-butyl]-4- methoxy-1H-indole-2-carboxamide

[000367] To a mixture of N-[(1S)-1-[[(1S)-2-amino-1-[(3-methylimidazol-4-yl)methyl]-2-oxo-ethyl]carb amoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (140 mg, 308.02 umol, 1 *eq*) in DCM (2 mL) was added Burgess reagent (293.61 mg, 1.23 mmol, 4 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h, and then concentrated to get the crude product. The crude product was purified by pre-HPLC. N-[(1S)-1-[[(1S)-1-cyano-2-(3-methylimidazol-4-yl)ethyl]carbamoyl]-3-methyl-butyl]-4- methoxy-1H-indole-2-carboxamide (10.59 mg, 23.82 umol, 7.73% yield, 98.2% purity) was obtained as a solid. MS (ESI) *m/z* 437.2 $[M+H]^+$.

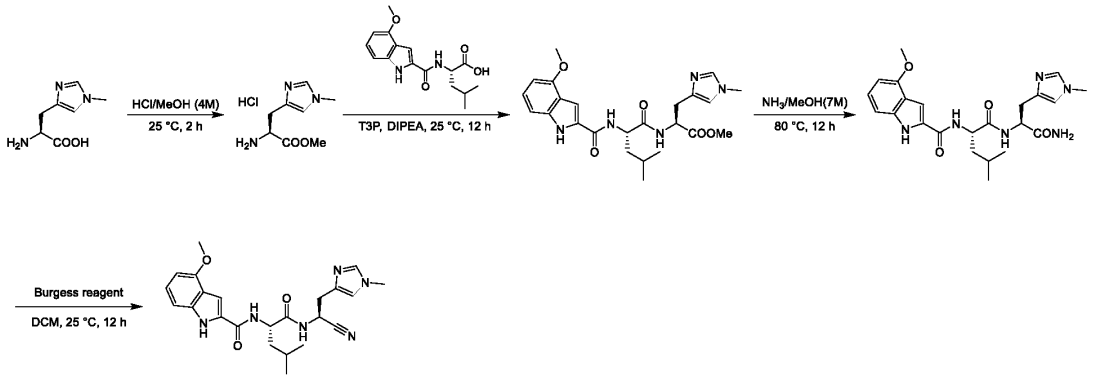
Prep-HPLC condition:

column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10mM NH_4HCO_3) -ACN];B%: 25%-50%,6min

column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3) -ACN];B%: 20%-45%,8min

[000368] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.52 - 7.57 (m, 1 H), 7.28 (s, 1 H), 7.12 - 7.18 (m, 1 H), 7.03 (d, *J*=8.38 Hz, 1 H), 6.85 - 6.96 (m, 1 H), 6.52 (d, *J*=7.72 Hz, 1 H), 5.05 - 5.13 (m, 1 H), 4.55 - 4.62 (m, 1 H), 3.86 - 3.99 (m, 3 H), 3.68 (s, 3 H), 3.21 (tt, *J*=15.24, 7.80 Hz, 2 H), 1.55 - 1.81 (m, 3 H), 0.86 - 1.07 (m, 6 H)

Example 25. Synthesis of viral protease inhibitor compound 227



Step 1: methyl (2S)-2-amino-3- (1-methylimidazol-4-yl)propanoate

[000369] To a mixture of (2S)-2-amino-3-(1-methylimidazol-4-yl)propanoic acid (0.5 g, 2.96 mmol, 1 *eq*) was added HCl/MeOH (4 M, 7.39 mL, 10 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to get the product. Methyl (2S)-2-amino-3- (1-methylimidazol-4-yl)propanoate (0.6 g, crude, HCl) was obtained as a solid and used directly next step. MS (ESI) *m/z* 184.1 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-[(4-methoxy -1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino] -3-(1-methylimidazol-4-yl)propanoate

[000370] To a mixture of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (498.76 mg, 1.64 mmol, 1.2 *eq*) and methyl (2S)-2-amino-3-(1-methylimidazol-4-yl)propanoate (0.3 g, 1.37 mmol, 1 *eq*, HCl), DIPEA (882.53 mg, 6.83 mmol, 1.19 mL, 5 *eq*) in THF (0.9 mL) and DCM (0.9 mL) was added T3P (1.30 g, 2.05 mmol, 1.22 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added to saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was washed with brine (3 mL * 3) and dried over anhydrous sodium sulfate and concentrated to get the crude product. The residue was purified by prep-HPLC. Methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-(1-methylimidazol-4-yl)propanoate (100 mg, 202.97 umol, 14.86% yield, 95.3% purity) was obtained as a solid. MS (ESI) *m/z* 470.2 $[M+H]^+$

Prep-HPLC condition:

column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25% - 50%,10min

Step 3: N-[(1S)-1-[[(1S)-2-amino-1-[(1-methylimidazol-4-yl)methyl]-2-oxo-ethyl]carbamoyl]-3-methyl -butyl]-4-methoxy-1H-indole-2-carboxamide

[000371] To methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino] -3-(1-methylimidazol-4-yl)propanoate (100 mg, 212.98 umol, 1 *eq*) was added NH_3/MeOH (7 M, 10.00 mL, 328.67 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to 25 °C and concentrated to get the product. N-[(1S)-1- [[(1S)-2-amino-1-[(1-methylimidazol-4-yl)methyl]-2-oxo-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (95.5 mg, 190.57 umol, 89.48% yield, 90.7% purity) was obtained as a solid and used directly next step. MS (ESI) *m/z* 455.2 $[M+H]^+$

Step 4: N-[(1S)-1-[[(1S)-1-cyano-2-(1-methylimidazol-4-yl)ethyl] carbamoyl]-3-methyl-butyl]-4- methoxy- 1H-indole-2-carboxamide

[000372] To a mixture of N-[(1S)-1-[[(1S)-2-amino-1-[(1-methylimidazol-4-yl)methyl]-2-oxo-ethyl]carba moyl]-3-methyl-butyl]-4-methoxy-1H-indole- 2- carboxamide (80.00 mg, 176.01 umol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (83.89 mg, 352.02 umol, 2 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added the water (0.3 mL) and stirred for 10 min. Then the reaction mixture was concentrated to get the crude product. The crude product was purified by prep-HPLC. N-[(1S)-1-[[(1S)-1-cyano-2-(1-methylimidazol-4-yl)ethyl] carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (26.39 mg, 60.27 umol, 34.24% yield, 99.684% purity) was obtained as a solid. MS (ESI) *m/z* 437.2 $[M+H]^+$

Prep-HPLC condition:
column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3) -ACN] ;B%: 25%-55%,10min

[000373] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.35 (s, 1 H), 7.28 (s, 1 H), 7.12 - 7.20 (m, 1 H), 7.05 (d, J = 8.38 Hz, 1 H), 6.91 - 6.98 (m, 1 H), 6.53 (d, J = 7.72 Hz, 1 H),

5.01 (t, *J* = 7.06 Hz, 1 H), 4.63 (br dd, *J* = 9.59, 4.96 Hz, 1 H), 3.94 (s, 3 H), 3.46 - 3.59 (m, 3 H), 3.00 - 3.13 (m, 2 H), 1.61 - 1.81 (m, 3 H), 0.89 - 1.07 (m, 6 H)

Step 5: tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate

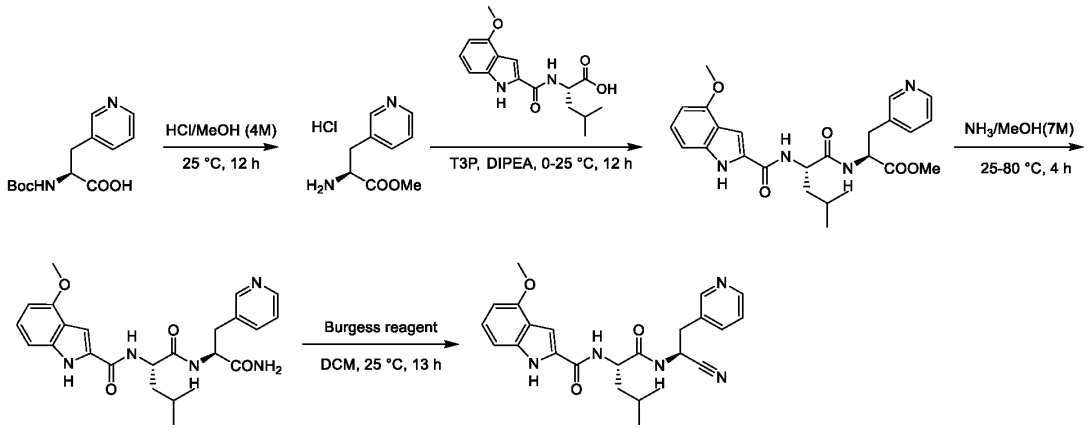
[000374] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (5 g, 26.15 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (5.88 g, 31.38 mmol, 1.2 *eq*, HCl), EDCI (6.52 g, 34.00 mmol, 1.3 *eq*), HOBt (4.59 g, 34.00 mmol, 1.3 *eq*) in DMF (30 mL) was added TEA (7.94 g, 78.46 mmol, 10.92 mL, 3 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was added water (90 mL) and extracted with EtOAc (25 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (25 mL) and 5% aqueous solution of sodium bicarbonate (25 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the product. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 30:1 to 10:1). Tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate (5.93 g, 16.45 mmol, 62.91% yield) was obtained as solid. MS (ESI) *m/z* 361.2 $[M+H]^+$

[000375] ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.25 (br s, 1 H), 7.10 - 7.16 (m, 1 H), 6.93 - 7.00 (m, 2 H), 6.56 (br d, *J* = 8.31 Hz, 1 H), 6.44 (d, *J* = 7.70 Hz, 1 H), 4.66 (td, *J* = 8.50, 5.14 Hz, 1 H), 3.88 (s, 3 H), 1.62 - 1.75 (m, 2 H), 1.57 - 1.62 (m, 1 H), 1.42 (s, 9 H), 0.92 (dd, *J* = 6.17, 3.85 Hz, 6 H).

Step 6: (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid

[000376] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (2.00 g, 5.55 mmol, 1 *eq*) in DCM (8 mL) was added TFA (10.27 g, 90.04 mmol, 6.67 mL, 16.23 *eq*) and H_2O (666.67 mg, 37.01 mmol, 666.67 uL, 6.67 *eq*) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C and stirred for 4 h. The reaction mixture was concentrated to get the crude product. (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (2.24 g, 5.35 mmol, 96.50% yield, TFA) was obtained as a solid and used directly next step. MS (ESI) *m/z* 305.1 $[M+H]^+$

Example 26. Synthesis of viral protease inhibitor compound 231



Step 1: (S)-methyl 2-amino-3-(pyridin-3-yl)propanoate hydrochloride

[000377] To a mixture of (2S)-2-(tert-butoxycarbonylamino)-3-(3-pyridyl)propanoic acid (500 mg, 1.88 mmol, 1 *eq*) was added HCl/MeOH (4 M, 20.80 mL, 44.31 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 12 h. Upon completion, the reaction mixture was concentrated to get methyl (2S)-2-amino-3-(3-pyridyl)propanoate (400 mg, crude, HCl) as an oil and used directly for the next step. MS (ESI) *m/z* 181.1 $[M+H]^+$

Step 2: (S)-methyl 2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-(pyridine -3-yl)propanoate

[000378] To a mixture of methyl (2S)-2-amino-3-(3-pyridyl)propanoate (0.3 g, 1.66 mmol, 1 *eq*, HCl) and (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (506.66 mg, 1.66 mmol, 1 *eq*), DIPEA (1.08 g, 8.32 mmol, 1.45 mL, 5 *eq*) in THF (0.6 mL) and DCM (0.6 mL) was added T_3P (1.59 g, 2.50 mmol, 1.49 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. Upon completion, the reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was concentrated to get the crude product. The residue was purified by pulping with petroleum ether (20 mL) and filtered to get the filter cake as the product. Methyl (2S)-2-[[(2S)-2-[(4-methoxy -1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-(3-pyridyl)propanoate (0.4 g, crude) was obtained as a solid and used directly next step. MS (ESI) *m/z* 467.1 $[M+H]^+$

Step 3: N-((S)-1-(((S)-1-amino-1-oxo-3-(pyridin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl) -4-methoxy-1H-indole-2-carboxamide

[000379] To a mixture of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl -pentanoyl]amino]-3-(3-pyridyl)propanoate (200.00 mg, 428.70 umol, 1 *eq*) was added NH_3/MeOH (7 M, 5 mL, 81.64 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 4 h. Upon completion, the reaction mixture was cooled to 25 °C and concentrated to get N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-(3-pyridylmethyl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (0.18 g, 339.65 umol, 79.23% yield, 85.2% purity) as a solid and used directly next step. MS (ESI) *m/z* 452.2 $[M+H]^+$

Step 3: N-((S)-1-(((S)-1-cyano-2-(pyridin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H -indole-2-carboxamide

[000380] To a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-(3-pyridylmethyl)ethyl]carbamoyl]-3-methyl -butyl]-4-methoxy-1H-indole-2-carboxamide (0.1 g, 221.48 umol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (105.56 mg, 442.95 umol, 2 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The Burgess reagent (105.56 mg, 442.95 umol, 2 *eq*) was re-added into the above solution at 25 °C and the reaction mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was added the water (0.5 mL) and stirred for 10 min. Then the mixture was concentrated to get the crude product. The crude product was purified by pre-HPLC to give N-[(1S)-1-[[(1S)-1-cyano-2-(3-pyridyl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (23.18 mg, 52.94 umol, 23.90% yield, 99.009% purity) as a solid. MS (ESI) *m/z* 434.2 $[M+H]^+$

Prep-HPLC condition:
column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min

[000381] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.47 - 8.52 (m, 1 H), 8.34 - 8.45 (m, 1 H), 7.77 - 7.84 (m, 1 H), 7.28 - 7.38 (m, 1 H), 7.23 - 7.28 (m, 1 H), 7.12 - 7.19 (m, 1 H), 6.99 - 7.07 (m, 1 H), 6.52 (d, J = 7.63 Hz, 1 H), 5.08 - 5.18 (m, 1 H), 4.48 - 4.61 (m, 1 H), 3.94 (s, 3 H), 3.12 - 3.29 (m, 2 H), 1.41 - 1.76 (m, 3 H), 0.87 - 1.03 (m, 6 H).

Step 5: (S)-tert-butyl 2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoate

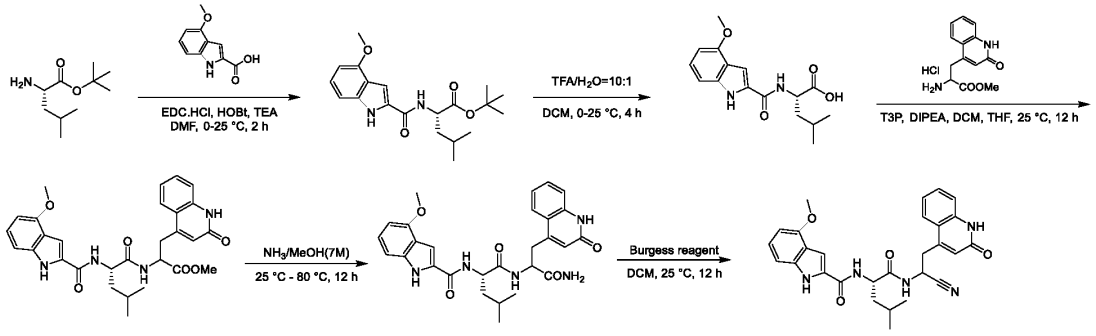
[000382] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (5 g, 26.15 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (5.88 g, 31.38 mmol, 1.2 *eq*, HCl), EDCI (6.52 g, 34.00 mmol, 1.3 *eq*), HOBt (4.59 g, 34.00 mmol, 1.3 *eq*) in DMF (30 mL) was added TEA (7.94 g, 78.46 mmol, 10.92 mL, 3 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. Upon completion, the reaction mixture was added water (90 mL) and extracted with ethyl acetate (25 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (25 mL) and 5% aqueous solution of sodium bicarbonate (25 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the crude product. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 30:1 to 10:1) to give tert-butyl (2S)-2-[(4-methoxy-1H-indole- 2-carbonyl)amino]-4-methyl-pentanoate (5.93 g, 16.45 mmol, 62.91% yield) as a solid. MS (ESI) *m/z* 361.2 $[M+H]^+$

[000383] ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.25 (br s, 1 H), 7.10 - 7.16 (m, 1 H), 6.93 - 7.00 (m, 2 H), 6.56 (br d, *J* = 8.31 Hz, 1 H), 6.44 (d, *J* = 7.70 Hz, 1 H), 4.66 (td, *J* = 8.50, 5.14 Hz, 1 H), 3.88 (s, 3 H), 1.62 - 1.75 (m, 2 H), 1.57 - 1.62 (m, 1 H), 1.42 (s, 9 H), 0.92 (dd, *J* = 6.17, 3.85 Hz, 6 H).

Step 6: (S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoic acid

[000384] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (0.5 g, 1.39 mmol, 1 *eq*) in DCM (0.33 mL) was added TFA (2.57 g, 22.51 mmol, 1.67 mL, 16.23 *eq*) and H_2O (166.71 mg, 9.25 mmol, 166.71 uL, 6.67 *eq*) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. Upon completion, the reaction mixture was concentrated to give (S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoic acid (400 mg, crude, TFA) as a solid and used directly next step. MS (ESI) *m/z* 305.1 $[M+H]^+$

Example 27. Synthesis of viral protease inhibitor compound 599



Step 1: tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate

[000385] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (5 g, 26.15 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (5.88 g, 31.38 mmol, 1.2 *eq*, HCl), EDCI (6.52 g, 34.00 mmol, 1.3 *eq*), HOBt (4.59 g, 34.00 mmol, 1.3 *eq*) in DMF (30 mL) was added TEA (7.94 g, 78.46 mmol, 10.92 mL, 3 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was added with water (90 mL) and extracted with EtOAc (25 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (25 mL) and 5% aqueous solution of sodium bicarbonate (25 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the product. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc= 30:1 to 10:1). Tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate (5.93 g, 16.45 mmol, 62.91% yield) was obtained as a solid. MS (ESI) *m/z* 361.2 $[M+H]^+$

[000386] ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.25 (br s, 1 H), 7.10 - 7.16 (m, 1 H), 6.93 - 7.00 (m, 2 H), 6.56 (br d, *J* = 8.31 Hz, 1 H), 6.44 (d, *J* = 7.70 Hz, 1 H), 4.66 (td, *J* = 8.50, 5.14 Hz, 1 H), 3.88 (s, 3 H), 1.62 - 1.75 (m, 2 H), 1.57 - 1.62 (m, 1 H), 1.42 (s, 9 H), 0.92 (dd, *J* = 6.17, 3.85 Hz, 6 H).

Step 2: (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid

[000387] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (2.00 g, 5.55 mmol, 1 *eq*) in DCM (8 mL) was added TFA (10.27 g, 90.04 mmol, 6.67 mL, 16.23 *eq*) and H_2O (666.67 mg, 37.01 mmol, 666.67 uL, 6.67 *eq*) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C and stirred for 4 h. The reaction mixture was concentrated to get the crude product. (2S)-2-[(4-methoxy-1H-

indole-2-carbonyl)amino]-4-methyl-pentanoic acid (2.24 g, 5.35 mmol, 96.50% yield, TFA) was obtained as a solid and used directly next step. MS (ESI) *m/z* 305.1 $[M+H]^+$

Step 3: methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3- (2-oxo-1H-quinolin-4-yl)propanoate

[000388] To a mixture of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (568.23 mg, 1.36 mmol, 1.2 *eq*, TFA) and methyl 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoate (320 mg, 1.13 mmol, 1 *eq*, HCl), DIPEA (731.40 mg, 5.66 mmol, 985.72 uL, 5 *eq*) in THF (1 mL) and DCM (1 mL) was added T3P (1.08 g, 1.70 mmol, 1.01 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added with saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was concentrated to get the crude product. The residue was purified by prep-HPLC. Methyl 2-[[(2S)-2-[(4-methoxy -1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-(2-oxo-1H-quinolin-4-yl)propanoate (0.2 g, 375.53 umol, 33.18% yield) was obtained as a solid. MS (ESI) *m/z* 533.2 $[M+H]^+$

[000389] Prep-HPLC condition: column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min

Step 4: N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-1H-quinolin-4-yl)methyl]ethyl]carbamoyl]-3-methyl- butyl]-4-methoxy-1H-indole-2-carboxamide

[000390] To a mixture ofmethyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl] amino]-3-(2-oxo-1H-quinolin-4-yl)propanoate (200.00 mg, 375.53 umol, 1 *eq*) was added NH_3/MeOH (7 M, 10.00 mL, 186.41 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to 25 °C and concentrated to get the product. N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-1H-quinolin-4-yl)methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (180 mg, 326.21 umol, 86.87% yield, 93.8% purity) was obtained as a solid and used directly next step. MS (ESI) *m/z* 518.2 $[M+H]^+$

Step 5: N-[(1S)-1-[[1-cyano-2-(2-oxo-1H-quinolin-4-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy- 1H-indole-2-carboxamide

[000391] To a mixture of N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-1H-quinolin-4-yl)methyl]ethyl]carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (90 mg, 173.89 umol, 1 *eq*) in DCM (5 mL) was added Burgess reagent (207.19 mg, 869.44 umol, 5 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h, and then concentrated to get the crude product.

[000392] The residue was purified by prep-HPLC. N-[(1S)-1-[[1-cyano-2-(2-oxo-1H-quinolin-4-yl)ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (20.74 mg, 41.13 umol, 23.66% yield, 99.079% purity) was obtained as a solid. MS (ESI) *m/z* 500.2 $[M+H]^+$

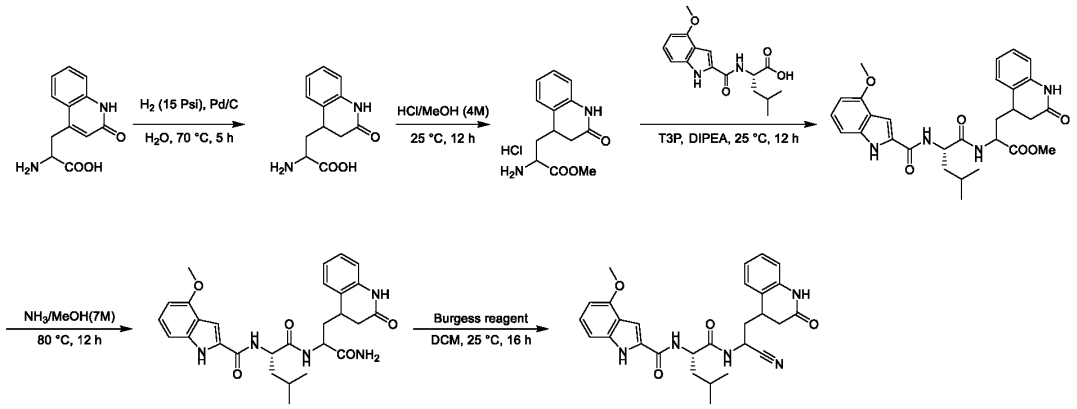
[000393] Prep-HPLC condition: column: Waters Xbridge BEH C18 100*25mm*5um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-65%, 10 min

[000394] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.93 (br d, *J* = 8.16 Hz, 1 H), 7.50 - 7.58 (m, 1 H), 7.28 - 7.40 (m, 2 H), 7.26 (dd, *J* = 11.47, 0.66 Hz, 1 H), 7.11 - 7.19 (m, 1 H), 7.04 (dd, *J* = 8.27, 4.08 Hz, 1 H), 6.59 - 6.70 (m, 1 H), 6.46 - 6.56 (m, 1 H), 5.24 - 5.34 (m, 1 H), 4.53 (td, *J* = 10.31, 5.18 Hz, 1 H), 3.93 (d, *J* = 4.41 Hz, 3 H), 3.40 - 3.59 (m, 3 H), 1.72 (ddd, *J* = 15.16, 9.87, 5.18 Hz, 1 H), 1.53 - 1.66 (m, 2 H), 1.40 - 1.50 (m, 1 H), 0.87 - 1.01 (m, 5 H)

Step 6: methyl 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoate

[000395] To 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoic acid (400 mg, 1.72 mmol, 1 *eq*) was added HCl/MeOH (4 M, 4.31 mL, 10 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 1 h. The reaction mixture was concentrated to get the product. Methyl 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoate (370 mg, crude, HCl) was obtained as a solid and used directly next step.

Example 28. Synthesis of viral protease inhibitor compound 249



Step 1: 2-amino-3-(2-oxo-3,4-dihydro-1H-quinolin-4-yl)propanoic acid

[000396] To a solution of 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoic acid (200 mg, 861.20 umol, 1 *eq*) in H_2O (1 mL) was added Pd/C (20 mg, 861.20 umol, 10% purity) at 25 °C under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (861.20 umol) (15psi) at 70 °C for 5 h. The reaction mixture was cooled to 25 °C and filtered to get the filtrate. The filtrate was concentrated to get the product. 2-amino-3-(2-oxo-3,4-dihydro-1H- quinolin-4-yl)propanoic acid (200 mg, crude) was obtained as a solid and used directly next step. MS (ESI) *m/z* 235.0 $[M+H]^+$

[000397] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 1.92 - 2.03 (m, 1 H) 2.06 - 2.21 (m, 1 H) 2.45 - 2.62 (m, 1 H) 2.86 (dd, *J* = 16.43, 6.06 Hz, 1 H) 3.32 - 3.40 (m, 1 H) 3.83 (br dd, *J* = 8.49, 5.84 Hz, 1 H) 3.93 (br t, *J* = 6.95 Hz, 1 H) 6.93 (d, *J* = 7.72 Hz, 1 H) 7.01 - 7.10 (m, 1 H) 7.24 (br t, *J* = 7.72 Hz, 1 H) 7.36 (d, J=7.06 Hz, 1 H)

Step 2: methyl 2-amino-3-(2-oxo-3,4-dihydro-1H-quinolin-4-yl)propanoate

[000398] To 2-amino-3-(2-oxo-3,4-dihydro-1H-quinolin-4-yl)propanoic acid (200 mg, 853.79 umol, 1 *eq*) was added HCl/MeOH (4 M, 9.91 mL, 46.45 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to get the crude product. Methyl 2-amino-3-(2-oxo-3,4-dihydro-1H-quinolin-4-yl)propanoate (260 mg, crude, HCl) was obtained as the yellow oil and used directly next step. MS (ESI) *m/z* 249.1 $[M+H]^+$

Step 3: methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3- (2-oxo-3,4-dihydro-1H-quinolin-4-yl)propanoate

[000399] To a mixture of methyl 2-amino-3-(2-oxo-3,4-dihydro-1H-quinolin-4-yl)propanoate (260 mg, 913.12 umol, 1 *eq*, HCl) and (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (277.90 mg, 913.12 umol, 1 *eq*), DIPEA (590.07 mg, 4.57 mmol, 795.24 uL, 5 *eq*) in THF (0.6 mL) and DCM (0.6 mL) was added T_3P (871.61 mg, 1.37 mmol, 814.59 uL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was concentrated to get the crude product. The residue was purified by pre-HPLC. Methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-(2-oxo -3,4-dihydro-1H-quinolin-4-yl)propanoate (85 mg, 151.05 umol, 16.54% yield, 95% purity) was obtained as a solid. MS (ESI) *m/z* 535.2 $[M+H]^+$

[000400] \Prep-HPLC condition: column: Phenomenex Gemini-NX 80*40 mm*3 um;mobile phase: [water(10 mM NH4HCO3)- ACN];B%: 27%-47%,8 min

Step 4: N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-3,4-dihydro-1H-quinolin-4-yl)methyl]ethyl]carbamoyl] -3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000401] To a mixture of methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl] amino]-3-(2-oxo-3,4-dihydro-1H-quinolin-4-yl)propanoate (55 mg, 102.88 umol, 1 *eq*) was added NH_3/MeOH (7 M, 1.83 mL, 124.74 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to the 25 °C and concentrated to get the product. N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-3,4-dihydro-1H-quinolin-4-yl)methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (55 mg, crude) was obtained as a solid and used directly next step. MS (ESI) *m/z* 518.2 $[M+H]^+$

Step 5: N-[(1S)-1-[[1-cyano-2-(2-oxo-1H-quinolin-4-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy- 1H-indole-2-carboxamide

[000402] To a mixture of N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-3,4-dihydro-1H-quinolin-4-yl)methyl]ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (75 mg, 144.34 umol, 1 *eq*) in DCM (0.1 mL) was added Burgess reagent (103.19 mg, 433.03 umol, 3 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 16 h. The reaction mixture was added with water (0.5 mL) and stirred for 10

min. Then the mixture was concentrated to get the crude product. The crude product was purified by pre-HPLC. N-[(1S)-1-[[1-cyano-2-(2-oxo-3,4-dihydro-1H- quinolin-4-yl) ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (26.51 mg, 52.85 umol, 36.62% yield, 100% purity) was obtained as a solid. MS (ESI) *m/z* 502.2 $[M+H]^+$

[000403] Prep-HPLC condition: column: Waters Xbridge BEH C18 100*25mm*5 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-60%,10 min

[000404] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.51 - 11.61 (m, 1 H), 10.14 - 10.20 (m, 1 H), 8.84 - 9.01 (m, 1 H), 8.42 - 8.59 (m, 1 H), 7.32 - 7.42 (m, 1 H), 7.05 - 7.22 (m, 3 H), 6.81 - 7.04 (m, 3 H), 6.50 (dd, *J* = 7.64, 3.85 Hz, 1 H), 4.37 - 4.66 (m, 2 H), 3.83 - 3.95 (m, 3 H), 2.95 - 3.12 (m, 1 H), 2.63 - 2.82 (m, 1 H), 2.26 - 2.42 (m, 1 H), 1.88 - 2.08 (m, 2 H), 1.45 - 1.82 (m, 3 H), 0.81 - 1.02 (m, 6 H)

Step 6: (S)-tert-butyl 2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoate

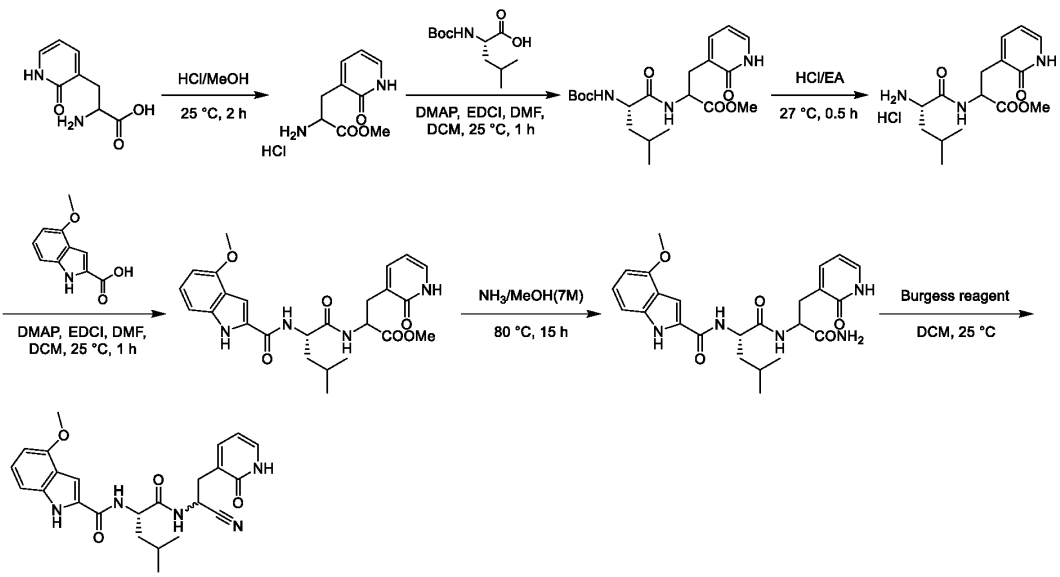
[000405] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (15 g, 78.46 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (21.07 g, 94.15 mmol, 1.2 *eq*, HCl) in DMF (150 mL) was added EDCI (19.55 g, 102.00 mmol, 1.3 *eq*), HOBt (13.78 g, 102.00 mmol, 1.3 *eq*), TEA (23.82 g, 235.38 mmol, 32.76 mL, 3 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was added water (450 mL) and extracted with EtOAc (250 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (300 mL) and 5% aqueous solution of sodium bicarbonate (300 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the product. The residue was purified by column chromatography (SiO_2, petroleum ether: EtOAc=30:1 to 10:1). tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate (24 g, 66.58 mmol, 84.87% yield) was obtained as a solid. MS (ESI) *m/z* 361.2 $[M+H]^+$

Step 7: (S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoic acid

[000406] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (10 g, 27.74 mmol, 1 *eq*) in DCM (30 mL) was added TFA (61.60 g, 540.26 mmol, 40 mL, 19.47 *eq*) and H_2O (4.00 g, 221.98 mmol, 4.00 mL, 8.00 *eq*) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to get the crude product. The crude product was purified with

petroleum ether:ethyl acetate = 10:1(20 mL) and filtered to get the product. (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (6 g, 19.22 mmol, 69.27% yield, 97.48% purity) was obtained as a solid. MS (ESI) *m/z* 305.1 $[M+H]^+$

Example 29. Synthesis of viral protease inhibitor compound 600



Step 1: methyl 2-amino-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate

[000407] A mixture of 2-amino-3-(2-oxo-1H-pyridin-3-yl)propanoic acid (500 mg, 2.74 mmol, 1 *eq*) and HCl/MeOH (4 M, 30 mL, 43.72 *eq*) was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a product methyl 2-amino-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (650 mg, crude, HCl) as a yellow oil and used directly for next step. MS (ESI) *m/z* 197.0 $[M+H]^+$

Step 2: methyl-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate

[000408] A mixture of methyl 2-amino-3-(2-oxo-1H-pyridin-3-yl)propanoate (650 mg, 2.79 mmol, 1 *eq*, HCl), (2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoic acid (646.16 mg, 2.79 mmol, 1 *eq*), EDCI (1.07 g, 5.59 mmol, 2 *eq*), DMAP (682.62 mg, 5.59 mmol, 2 *eq*), DMF (2 mL) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered

and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc= 0/1) to get the product methyl-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (900 mg, 1.89 mmol, 67.68% yield, 86.02% purity), as a solid. MS (ESI) *m/z* 410.1 $[M+H]^+$

Step 3: methyl 2-((S)-2-amino-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate

[000409] A mixture of methyl-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (200 mg, 488.43 umol, 1 *eq*) and HCl/EtOAc (4 M, 30 mL) was stirred at 27 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a product methyl 2-((S)-2-amino-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (170 mg, crude, HCl) as a solid and used directly for next step.

Step 4: methyl 2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate

[000410] A mixture of methyl 2-((S)-2-amino-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (170 mg, 491.58 umol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (93.98 mg, 491.58 umol, 1 *eq*), EDCI (188.47 mg, 983.17 umol, 2 *eq*), DMAP (120.11 mg, 983.17 umol, 2 *eq*), DMF (2 mL) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc= 0/1) to get the compound methyl 2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (130 mg, 269.41 umol, 54.81% yield), as a solid. MS (ESI) *m/z* 483.1 $[M+H]^+$

Step 5: N-((2S)-1-((1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000411] A mixture of methyl 2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (190 mg, 393.76 umol, 1 *eq*), NH_3/MeOH (7 M, 10 mL) was stirred at 80 °C for 15 h. The reaction mixture

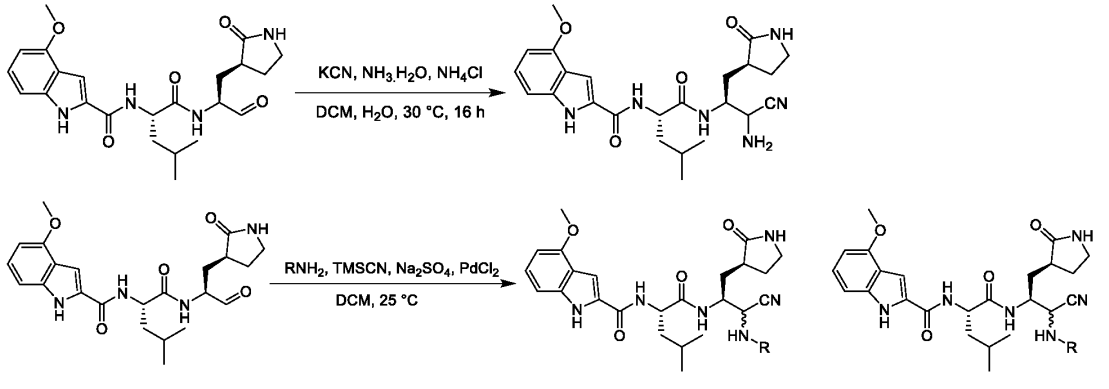
was concentrated under reduced pressure to give N-((2S)-1-((1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (190 mg, crude) as a solid. MS (ESI) *m/z* 468.2 $[M+H]^+$

Step 6: N-((2S)-1-((1-cyano-2-(2-oxo-1,2-dihydropyridin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000412] A mixture of N-((2S)-1-((1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (180 mg, 385.01 umol, 1 *eq*), Burgess reagent (917.53 mg, 3.85 mmol, 10 *eq*) and DCM (30 mL) was stirred at 25 °C for 8 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 25%-45%,8min) to get the product N-((2S)-1-((1-cyano-2-(2-oxo-1,2-dihydropyridin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (24 mg, 52.18 umol, 13.55% yield, 97.73% purity), as a solid. MS (ESI) *m/z* 450.2 $[M+H]^+$.

[000413] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.90-11.40 (m, 2H), 9.08 - 8.85 (m, 1H), 8.55 - 8.35 (m, 1H), 7.51 - 7.26 (m, 3H), 7.16 - 7.05 (m, 1H), 7.04 - 6.94 (m, 1H), 6.51 (d, J=7.5 Hz, 1H), 6.15 (t, J=6.6 Hz, 1H), 5.19 - 5.01 (m, 1H), 4.55 - 4.33 (m, 1H), 3.89 (s, 3H), 3.02 - 2.78 (m, 2H), 1.75 - 1.33 (m, 3H), 0.98 - 0.72 (m, 6H)

Example 30. Synthesis of viral protease inhibitor compounds 344C, 344D, 507 and 511



Step for compound 344C: N-[(1S)-1-[[(1S)-2-amino-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000414] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl- butyl]-4-methoxy-1H-indole-2-carboxamide (100 mg, 180.79 umol, 80% purity, 1 eq) in DCM (10 mL) was added $NH_3.H_2O$ (46.93 mg, 361.58 umol, 51.57 uL, 27% purity, 2 eq) and NH_4Cl (19.34 mg, 361.58 umol, 2 eq). The mixture was stirred at 25 °C for 30 min, then added KCN (94.18 mg, 1.45 mmol, 61.96 uL) in H_2O (0.2 mL) , the mixture was stirred at 30 °C for 16 h. Once the reaction was completed, the reaction mixture was then quenched by addition H_2O (10 mL) at 0 °C, and then diluted with H_2O (10 mL) and extracted with EtOAc (30 mL * 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The liquid water was added with NaOH to adjust pH=9, quenched with aq NaCl, and then added with NaOH to adjust pH > 14. The residue was purified by HCl prep-HPLC to get the compound N-[(1S)-1-[[(1S)-2-amino-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (50 mg, 103.83 umol, 57.43% yield, 97.3% purity) as a solid. MS (ESI) *m/z* 469.2 $[M+H]^+$

prep-HPLC condition:

column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.04%HCl)-ACN]; B%: 15% - 40%,7min

[000415] ^1H NMR (400MHz, DMSO-*d6*) δ = 11.59 (dd, *J*=1.9, 5.0 Hz, 1H), 9.16 - 8.58 (m, 2H), 8.54 - 8.26 (m, 2H), 7.66 (d, *J*=9.0 Hz, 1H), 7.37 (dd, *J*=2.0, 4.2 Hz, 1H), 7.14 - 7.06 (m, 1H), 7.04 - 6.97 (m, 1H), 6.51 (d, *J*=7.5 Hz, 1H), 4.61 - 4.42 (m, 2H), 4.39 - 4.21 (m, 1H), 3.88 (s, 3H), 3.20 - 2.98 (m, 2H), 2.48 - 2.34 (m, 1H), 2.14 - 1.88 (m, 2H), 1.82 - 1.47 (m, 5H), 0.92 (dd, *J*=6.0, 14.8 Hz, 6H)

Step for compound 511: N-[(1S)-1-[[(1S) -2-cyano-2-(ethylamino)-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000416] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl- butyl]-4-methoxy-1H-indole-2-carboxamide (80 mg, 108.47 umol, 60% purity, 1 eq) in DCM (5 mL) was added $PdCl_2$ (3.85 mg, 21.69 umol, 0.2 eq), Na_2SO_4 (53.93 mg, 379.66 umol, 38.52 uL, 3.5 eq), and ethanamine (9.78 mg,

216.95 umol, 14.19 uL, 2 eq). The resulting mixture was stirred at 25 °C for 30 min, and then added with TMSCN (21.52 mg, 216.95 umol, 27.14 uL, 2 eq). The resulting mixture was stirred at 25 °C for 1 h. Once the reaction was completed, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by HCl prep-HPLC to yield 70 mg of the mixture. The mixture was purified by SFC to get the N-[(1S)-1-[[(1S)-2-cyano-2-(ethylamino)-1-[[(3S)-2-oxo pyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (16 mg, 28.20 umol, 26.00% yield, 87.525% purity) as an oil and N-[(1S)-1-[[(1S) -2-cyano-2-(ethylamino)-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (16 mg, 31.44 umol, 28.98% yield, 97.569% purity) as a solid. MS (ESI) *m/z* 497.3 $[M+H]^+$

Prep-HPLC condition:

column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.04%HCl)-ACN];B%: 25%-40%,7min

SFC condition:

column: DAICEL CHIRALCEL OX (250mm*30mm,10um);mobile phase: [Neu-ETOH];B%: 38% - 38%, 9min

[000417] Compound 511 Isomer 1 :^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.56 (br s, 1H), 8.37 (br d, *J*=7.7 Hz, 1H), 8.29 - 8.20 (m, 1H), 7.80 - 7.48 (m, 3H), 7.35 (br d, *J*=2.0 Hz, 1H), 7.17 - 6.96 (m, 2H), 6.50 (d, J=7.7 Hz, 1H), 4.53 - 4.40 (m, 1H), 4.05 (td, *J*=3.9, 7.7 Hz, 1H), 3.88 (s, 3H), 3.77 (br dd, *J*=4.9, 10.1 Hz, 1H), 3.18 - 2.97 (m, 2H), 2.88 - 2.63 (m, 2H), 2.40 - 2.24 (m, 1H), 2.14 - 2.06 (m, 2H), 1.82 - 1.31 (m, 5H), 1.09 - 0.98 (m, 3H), 0.91 (br dd, *J*=6.2, 16.1 Hz, 6H)

[000418] Compound 511 Isomer 2:^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.58 (d, *J*=1.5 Hz, 1H), 8.41 (br d, *J*=7.9 Hz, 1H), 8.17 (br s, 1H), 7.63 - 7.50 (m, 1H), 7.37 (d, *J*=1.8 Hz, 1H), 7.14 - 7.05 (m, 1H), 7.00 (d, *J*=8.2 Hz, 1H), 6.50 (d, *J*=7.5 Hz, 1H), 4.58 - 4.37 (m, 1H), 4.25 - 3.99 (m, 1H), 3.88 (s, 3H), 3.81 - 3.51 (m, 1H), 3.16 - 2.96 (m, 2H), 2.89 - 2.54 (m, 2H), 2.43 - 2.23 (m, 1H), 2.20 - 1.99 (m, 1H), 1.95 - 1.43 (m, 6H), 1.10 - 0.98 (m, 3H), 0.91 (dd, *J*=6.4, 15.2 Hz, 6H)

Step for compound 507: N-[(1S)-1-[[(1S)-2-(benzylamino)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

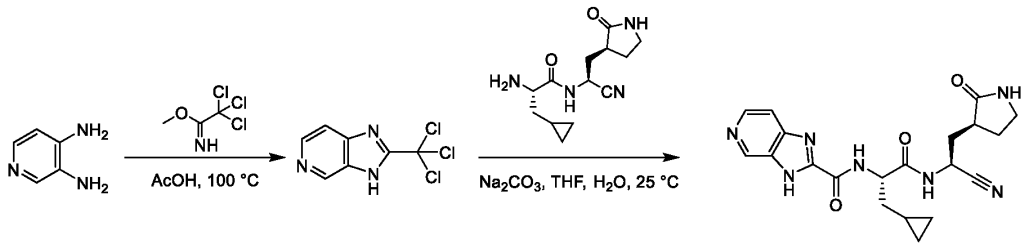
[000419] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl- butyl]-4-methoxy-1H-indole-2-carboxamide (150 mg, 271.18 umol, 80% purity, 1 eq) in DCM (15 mL) was added $PdCl_2$ (9.62 mg, 54.24 umol, 0.2 eq), Na_2SO_4 (134.82 mg, 949.14 umol, 96.30 uL, 3.5 eq) and $BnNH_2$ (58.11 mg, 542.36 umol, 59.12 uL, 2 eq). The mixture was stirred at 25 °C for 30 min, then added with TMSCN (53.81 mg, 542.36 umol, 67.85 uL, 2 eq). The mixture was stirred at 25 °C for 2 hours. Once the reaction was completed, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by HCl prep-HPLC to get the compound N-[(1S)-1-[[(1S)-2-(benzylamino)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (30 mg, 51.71 umol, 19.07% yield, 96.291% purity) and N-[(1S)-1-[[(1S)-2-(benzylamino)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (18 mg, 31.04 umol, 11.44% yield, 96.329% purity) as a solid. MS (ESI) *m/z* 559.3 $[M+H]^+$

Prep-HPLC condition:
column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.04%HCl)-ACN];B%: 38%-62%,7min

[000420] Compound 507 Isomer 1: ^{1}H NMR: (400MHz, DMSO-*d*6) δ = 11.58 (d, *J*=1.8 Hz, 1H), 8.48 - 8.34 (m, 1H), 8.23 (br d, *J*=9.5 Hz, 1H), 7.69 - 7.53 (m, 1H), 7.51 - 7.23 (m, 5H), 7.14 - 7.05 (m, 1H), 7.02 - 6.97 (m, 1H), 6.50 (d, *J*=7.7 Hz, 1H), 4.56 - 4.37 (m, 1H), 4.23 (br d, *J*=9.3 Hz, 1H), 4.13 - 3.91 (m, 2H), 3.88 (s, 3H), 3.84 (br d, *J*=13.2 Hz, 1H), 3.17 - 2.95 (m, 2H), 2.42 - 2.24 (m, 1H), 2.16 - 1.98 (m, 1H), 1.93 - 1.44 (m, 6H), 0.90 (dd, *J*=6.3, 16.2 Hz, 6H)

[000421] Compound 507 Isomer 2: ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.56 (br d, *J*=1.5 Hz, 1H), 8.52 - 8.14 (m, 2H), 7.69 - 7.55 (m, 1H), 7.49 - 7.22 (m, 6H), 7.13 - 7.05 (m, 1H), 7.00 (d, *J*=8.4 Hz, 1H), 6.50 (d, *J*=7.5 Hz, 1H), 4.56 - 4.41 (m, 1H), 4.21 (br s, 1H), 4.06 - 3.94 (m, 2H), 3.88 (s, 3H), 3.83 (br d, *J*=12.8 Hz, 1H), 3.17 - 2.97 (m, 2H), 2.42 - 2.29 (m, 1H), 2.17 - 2.00 (m, 2H), 1.83 - 1.44 (m, 5H), 0.90 (dd, *J*=6.3, 17.8 Hz, 6H)

Example 31. Synthesis of viral protease inhibitor compound 129



Step 1. 2-(trichloromethyl)-3H-imidazo[4,5-c]pyridine

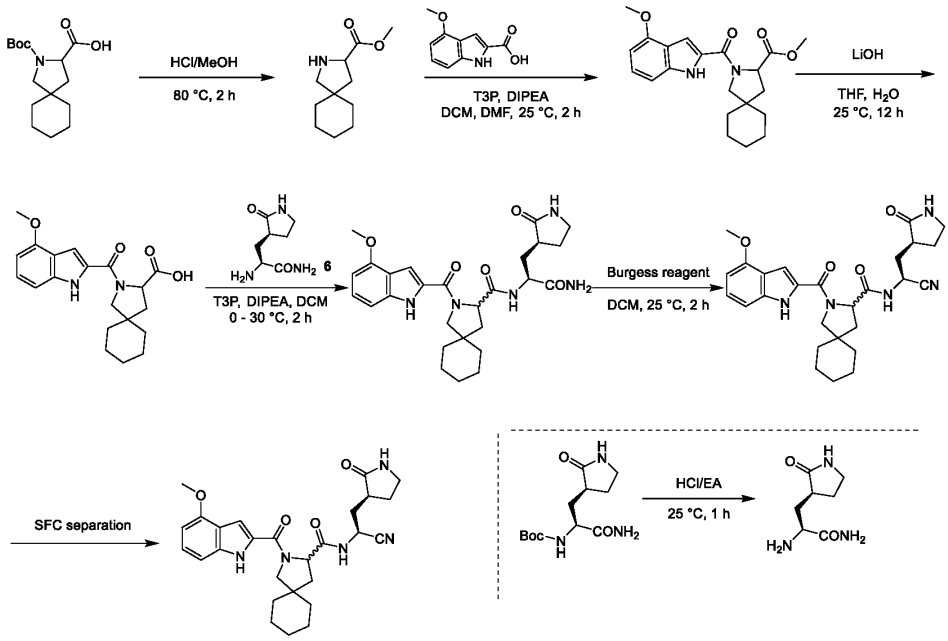
[000422] To a solution of pyridine-3,4-diamine (2 g, 18.33 mmol, 1 *eq*) in AcOH (25 mL) was added methyl 2,2,2-trichloroethanimidate (3.88 g, 21.99 mmol, 2.71 mL, 1.2 *eq*). The solution was stirred for 5 h at 100 °C. The reaction was added with H_2O (90 mL) and extracted with ethyl acetate (70 mL * 3) and washed with $NaHCO_3$ (90 mL * 2). The organic layer was cautiously concentrated to give crude 2-(trichloromethyl)-3H-imidazo[4,5-c]pyridine (800 mg, crude) was obtained as a yellow solid. The crude was used directly for the next step. MS (ESI) *m/z* 235.9 $[M+H]^+$

Step 2: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-3H-imidazo[4,5-c]pyridine-2-carboxamide

[000423] To a solution of 2-(trichloromethyl)-3H-imidazo[4,5-c]pyridine (150 mg, 634.29 umol, 1 *eq*) and (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide(167.66 mg, 634.29 umol, 1 *eq*) in THF (5 mL) and H_2O (2.5 mL) was added Na_2CO_3 (201.68 mg, 1.90 mmol, 3 *eq*). The solution was stirred for 1 h at 20 °C. The solution was added with H_2O (20 mL), extracted with ethyl acetate (40 mL * 3) and concentrated to give crude. The crude was purified by pre-HPLC(Column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 1%-23%, 8min) to give 70% purity product and then continue purified by pre-HPLC(Column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (0.2%FA)-ACN]; B%: 1%-30%, 8min) to give product N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-3H-imidazo[4,5-c]pyridine-2-carboxamide (3 mg, 6.96 umol, 1.10% yield, 95% purity) was obtained as a solid. MS (ESI) *m/z* 410.1 $[M+H]^+$. ^1H NMR (400MHz, DMSO-d_6) δ = 8.89 - 8.81 (m, 2H), 8.77 (d, *J*=7.9 Hz, 1H), 8.21 (d, *J*=5.4 Hz, 2H), 7.54 (s, 1H), 7.43 (br d, *J*=5.4 Hz, 1H), 4.91 - 4.76 (m, 1H), 4.44 - 4.32 (m, 1H), 3.02 - 2.92 (m, 2H), 2.25 - 2.16 (m, 1H),

2.03 - 1.91 (m, 2H), 1.78 - 1.38 (m, 4H), 0.59 (br s, 1H), 0.25 (br d, *J*=7.9 Hz, 2H), 0.05 - 0.11 (m, 2H).

Example 32. Synthesis of viral protease inhibitor compound 389A and 389B



Step 1: (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide

[000424] *tert*-Butyl *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamate (2 g, 7.37 mmol, 1 eq) in HCl/EtOAc (4 M, 50 mL, 27.13 eq) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (1.2 g, crude) as a solid.

Step 2: Methyl 2-azaspiro[4.5]decane-3-carboxylate

[000425] A solution of 2-*tert*-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (3 g, 10.59 mmol, 1 eq) in HCl/MeOH (4 M, 50 mL, 18.89 eq) was stirred at 80 °C for 2 h. The mixture was concentrated under the reduced pressure to afford the product methyl 2-azaspiro[4.5]decane-3-carboxylate (2 g, crude) as a yellow oil.

Step 3: Methyl 2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate

[000426] To a solution of methyl 2-azaspiro[4.5]decane-3-carboxylate (2 g, 10.14 mmol, 1 eq) and 4-methoxy-1*H*-indole-2-carboxylic acid (2.33 g, 12.17 mmol, 1.2 eq) in DCM (30 mL) and DMF (5 mL) was added T3P (12.90 g, 20.28 mmol, 12.06 mL, 50% purity, 2 eq) and DIEA (3.93 g, 30.41 mmol, 5.30 mL, 3 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (100 mL), and extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 10:1 to 0:1) to afford the product methyl 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate (3 g, 8.10 mmol, 79.88% yield) as a solid. MS (ESI) *m/z* 371.1 $[M+H]^+$

Step 4: 2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid

[000427] To a solution of methyl 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate (3 g, 8.10 mmol, 1 eq) in THF (45 mL) and H_2O (15 mL) was added $LiOH.H_2O$ (1.70 g, 40.49 mmol, 5 eq). The mixture was stirred at 25 °C for 12 h. Upon completion, the mixture was quenched by addition H_2O (50 mL), and then added aq. HCl (1 M) to adjust the pH = 3-4, and then extracted with ethyl acetate (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure affording the product 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (2.6 g, crude) as a white solid. MS (ESI) *m/z* 357.1 $[M+H]^+$

Step 5: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000428] To a solution of 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (1 g, 2.81 mmol, 1 eq) and (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (720.49 mg, 4.21 mmol, 1.5 eq) in DCM (30 mL) was added T3P (3.57 g, 5.61 mmol, 3.34 mL, 50% purity, 2 eq) and DIEA (1.09 g, 8.42 mmol, 1.47 mL, 3 eq) at 0 °C. The mixture was stirred at 30 °C for 1 h. Upon completion, the mixture was quenched by addition H_2O (100 mL), and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered

and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1:0 to 10:1) affording the product *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (700 mg, 1.37 mmol, 48.96% yield) as a white solid. MS (ESI) *m/z* 510.3 $[M+H]^+$

Step 6: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

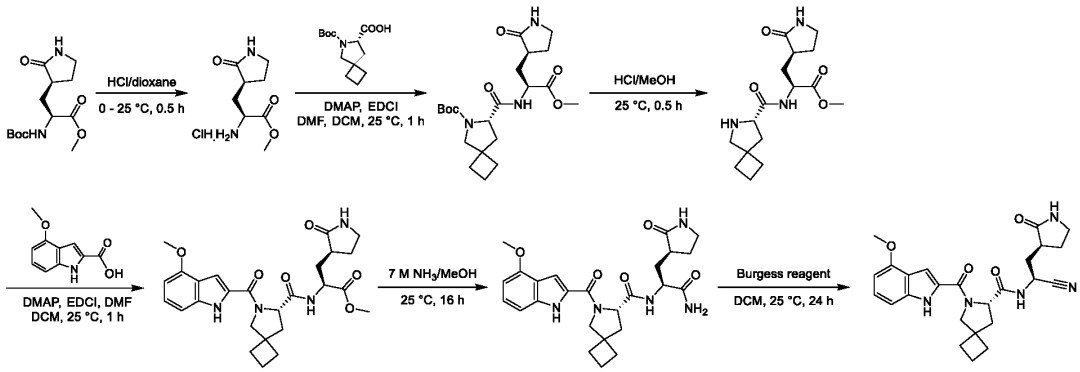
[000429] To a solution of *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (700 mg, 1.37 mmol, 1 eq) in DCM (10 mL) was added Burgess reagent (982.03 mg, 4.12 mmol, 3 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Kromasil C18 (250 * 50 mm * 10 um); mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 10 min) affording the product *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (500 mg, 1.02 mmol, 74.05% yield) as a white solid. MS (ESI) *m/z* 492.3 $[M+H]^+$

Step 7: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000430] *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (500 mg, 1.02 mmol) was separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O IPA]; B%: 55% - 55%, 9 min) to afford the product *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide, Isomer 1 (264 mg, 537.04 umol, 52.80% yield) as a solid. MS (ESI) *m/z* 492.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.28 - 6.76 (m, 3H), 6.60 - 6.38 (m, 1H), 5.05 (br dd, *J* = 5.2, 10.2 Hz, 1H), 4.63 – 4.60 (m, 1H), 4.03 - 3.85 (m, 5H), 3.74 - 3.28 (m, 1H), 2.73 (br dd, *J* = 5.0, 8.6 Hz, 1H), 2.51 - 2.28 (m, 2H), 2.27 - 2.08 (m, 1H), 1.96 - 1.72 (m, 2H), 1.69 - 1.38 (m, 11H), 1.37 - 1.09 (m, 1H); and

[000431] *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide, Isomer 2 (140 mg, 284.51 umol, 27.97% yield) as a solid. MS (ESI) *m/z* 492.3 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.30 - 6.81 (m, 3H), 6.53 (br d, *J* = 2.0 Hz, 1H), 5.12 - 4.95 (m, 2H), 4.70 - 4.55 (m, 2H), 4.08 - 3.86 (m, 4H), 3.84 - 3.72 (m, 1H), 2.62 - 2.40 (m, 1H), 2.36 - 2.18 (m, 2H), 1.94 - 1.69 (m, 3H), 1.68 - 1.34 (m, 11H).

Example 33. Synthesis of viral protease inhibitor compound 399



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[000432] To a solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (130 mg, 454.03 umol, 1 eq) in HCl/dioxane (4 M, 2.27 mL, 20 eq) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to get the product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (173.4 mg, 451.67 umol, 99.48% yield, HCl) was obtained as yellow liquid.

Step 2: (S)-tert-butyl 7-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate

[000433] To a solution of (7S)-6-tert-butoxycarbonyl-6-azaspiro[3.4]octane-7-carboxylic acid (105.34 mg, 412.59 umol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (158.4 mg, 412.59 umol, 1 eq, HCl) in DCM (1.2 mL) and DMF (0.4 mL) was added DMAP (100.81 mg, 825.19 umol, 2 eq) and EDCI (158.19 mg, 825.19 umol, 2 eq). The reaction mixture was stirred at 25 °C for 1 h. The residue was diluted with H_2O

(6 mL) and extracted with ethyl acetate (3 mL). The combined organic layers were washed with ethyl acetate (3 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate=0/1) to get the product tert-butyl (7S)-7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (66.3 mg, 156.55 umol, 37.94% yield) was obtained as a liquid. MS (ESI) *m/z* 424.0 $[M+H]^+$

Step 3: (S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-((S)-6-azaspiro[3.4]octane-7-carboxamido)propanoate

[000434] A solution of tert-butyl (7S)-7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (66.3 mg, 156.55 umol, 1 eq) in HCl/MeOH (4 M, 782.76 uL, 20 eq) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to get the product methyl (2S)-2-[[(7S)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (71.1 mg, 156.09 umol, 99.71% yield, 79% purity, HCl) was obtained as a yellow liquid.

Step 4: (S)-methyl 2-((S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000435] To a solution of methyl (2S)-2-[[(7S)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (62.8 mg, 137.87 umol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (26.36 mg, 137.87 umol, 1 eq) in DCM (1.2 mL) and DMF (0.4 mL) was added DMAP (33.69 mg, 275.74 umol, 2 eq) and EDCI (52.86 mg, 275.74 umol, 2 eq) at 25 °C for 1 h. The residue was diluted with brine (6 mL) and extracted with ethyl acetate (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate=0/1) to get the product methyl (2S)-2-[[(7S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (33.2 mg, 66.86 umol, 48.50% yield) was obtained as a white solid. MS (ESI) *m/z* 497.1 $[M+H]^+$

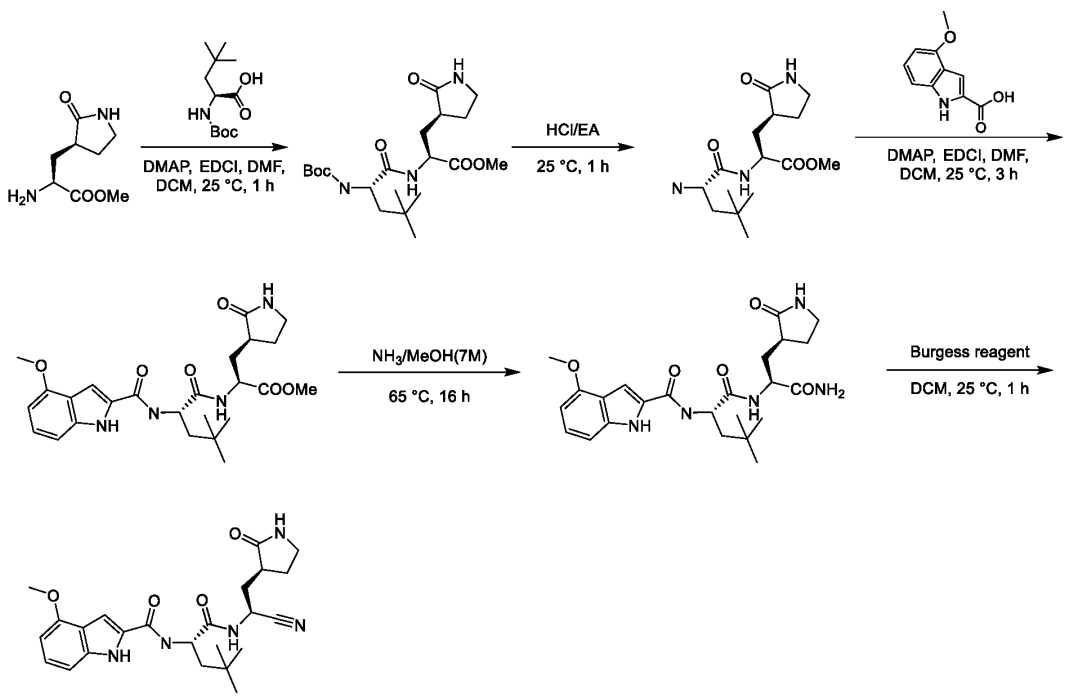
Step 5: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000436] A mixture of methyl (2S)-2-[[(7S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (23.0 mg, 46.32 umol, 1 eq) and ammonia (7 M, 4 mL, 604.50 eq) was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to get the product (7S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (15 mg, crude) was obtained as a yellow solid. MS (ESI) *m/z* 482.2 $[M+H]^+$

Step 6: (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000437] A solution of (7S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (15 mg, 28.66 umol, 1 eq) and Burgess reagent (13.66 mg, 57.32 umol, 2 eq) was stirred at 25 °C for 24 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30mm * 10um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 20% - 45%, 8min) to get the product (7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (3.01 mg, 6.49 umol, 22.66% yield) was obtained as a solid. MS (ESI) *m/z* 464.3 $[M+H]^+$ ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 6.95 - 7.24 (m, 3 H) 6.47 - 6.58 (m, 1 H) 5.01 (br dd, *J*=10.67, 5.19 Hz, 1 H) 4.58 (t, *J*=7.09 Hz, 1 H) 3.82 - 4.19 (m, 5 H) 3.19 (br t, *J*=8.52 Hz, 1 H) 2.93 - 3.07 (m, 1 H) 2.28 - 2.56 (m, 3 H) 2.16 - 2.27 (m, 2 H) 1.94 - 2.14 (m, 6 H) 1.47 - 1.86 (m, 2 H).

Example 34. Synthesis of viral protease inhibitor compound 405



Step 1: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000438] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (225 mg, 1.21 mmol, 1 *eq*) in DMF (2 mL) and DCM (4 mL) was added TEA (733.62 mg, 7.25 mmol, 1.01 mL, 6 *eq*) and T_3P (1.15 g, 3.62 mmol, 1.08 mL, 3 *eq*) and (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (296.42 mg, 1.21 mmol, 1 *eq*). The solution was stirred for 1 h at 25 °C. The reaction was added with H_2O (40 mL) and extracted with ethyl acetate (50 mL* 3) and the organic layer was cautiously concentrated to give crude compound methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (440 mg, crude) as a solid used directly for the next step. MS (ESI) *m/z* 414.1 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000439] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (440 mg, 1.06 mmol, 1 *eq*) in

HCl/MeOH (10 mL) was stirred for 1 h at 25 °C. TLC(DCM:MeOH = 10:1). The reaction was cautiously concentrated to give crude. Compound methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (310 mg, crude) as a solid used directly for the next step. MS (ESI) *m/z* 314.3 $[M+H]^+$

Step 3: methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000440] To a solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (310 mg, 989.18 umol, 1 *eq*) in DMF (4 mL) and DCM (4 mL) was added EDCI (379.25 mg, 1.98 mmol, 2 *eq*) and DMAP (241.70 mg, 1.98 mmol, 2 *eq*) and 4-methoxy-1H-indole-2-carboxylic acid (189.11 mg, 989.18 umol, 1 *eq*) was added. The solution was stirred for 3 h at 25 °C. The reaction was added with H_2O (40 mL) and extracted with ethyl acetate (80 mL* 3) and the organic layer was cautiously concentrated to give crude. The crude was purified by pre-TLC(SiO_2, ethyl acetate:MeOH=10:1) to afford methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 411.05 umol, 41.55% yield). MS (ESI) *m/z* 487.2 $[M-H]^+$

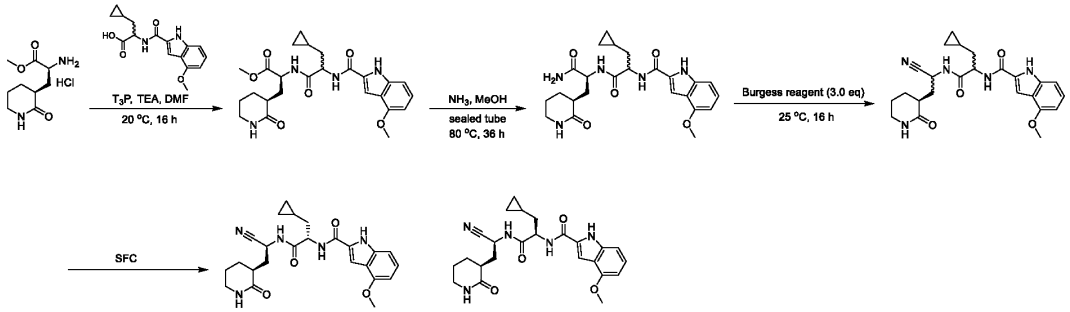
Step 4: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000441] A solution of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (135 mg, 277.46 umol, 1 *eq*) in NH_3/MeOH (7 M, 8 mL, 201.83 *eq*) was stirred for 16 h at 65 °C. The reaction was cautiously concentrated to give crude. Compound N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (130 mg, crude) as a solid used directly for the next step. MS (ESI) *m/z* 472.3 $[M+H]^+$; Prep-HPLC condition: column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 35%-55%, 8min

Step 5: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000442] To a solution of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (130 mg, 275.69 umol, 1 *eq*) in DCM (7 mL) was added Burgess reagent (197.09 mg, 827.06 umol, 3 *eq*) .The solution was stirred for 1 h at 25 °C. The reaction was cautiously concentrated to give crude. The crude was purified by pre-HPLC(TFA) to afford N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (36 mg, 75.41 umol, 27.35% yield, 95% purity) as a solid. MS (ESI) *m/z* 454.1 $[M+H]^+$. Prep-HPLC condition: column: Phenomenex luna C18 80*40 mm*3 um; mobile phase: [water(0.04% HCl)-ACN];B%: 30%-55%,7 min; ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 1.02 (s, 9 H) 1.74 - 1.94 (m, 4 H) 2.21 - 2.37 (m, 2 H) 2.52 - 2.63 (m, 1 H) 3.16 - 3.26 (m, 2 H) 3.92 (s, 3 H) 4.63 (dd, *J*=8.49, 4.30 Hz, 1 H) 4.98 - 5.06 (m, 1 H) 6.50 (d, *J*=7.72 Hz, 1 H) 7.02 (d, *J*=8.38 Hz, 1 H) 7.10 - 7.16 (m, 1 H) 7.23 (d, *J*=0.88 Hz, 1 H).

Example 35. Synthesis of viral protease inhibitor compound 491 and 491A



Step 1: Methyl (2S)-2-[[3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000443] To the mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 4.22 mmol, 1 *eq*,HCl),3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (1.5 g, 5.06 mmol, 1.2 *eq*, HCl) and TEA (1.7 g, 16.88 mmol, 2.35 mL, 4 *eq*) in DMF (5 mL) was added T_3P (5.3 g, 8.44 mmol, 5.02 mL, 50% purity, 2 *eq*) at 25°C. The mixture was stirred at 25°C for 16 h. TLC (DCM:MeOH =10:1/UV254nm) showed new spot was detected. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The

combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 100~25% Ethyl acetate/MeOH@ 30 mL/min). Compound methyl (2S)-2-[[3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.9 g, 3.84 mmol, 91.0% yield) was obtained as a solid. Methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (50 mg, 0.10 mmol, 1 *eq*) was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 20%-50%,9.5 min). Compound methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (50 mg, 0.10 mmol, 1 *eq*) was obtained as a solid.

Step 2: N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000444] The mixture of methyl (2S)-2-[[3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.00 g, 1.73 mmol, 84% purity, 1 *eq*) in NH_3 (7 M, 24.77 mL, 100 *eq*) (7M in MeOH) was stirred at 80 °C for 36 h. Then, the reaction mixture was concentrated in vacuum. Compound N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (813 mg, crude) was obtained as yellow solid.

[000445] N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (50 mg, 0.10 mmol, 1 *eq*) was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 23%-53%,7.8 min). Compound N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (20.3 mg, 42.5 umol, 39.9% yield, 98.4% purity) was obtained as white solid.

Step 3: N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000446] A mixture of N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (663.0 mg, 1.41 mmol, 1 *eq*) and methoxycarbonyl-(triethylammonio)sulfonyl-azanide (673.0 mg, 2.82 mmol, 2 *eq*) in DCM (8 mL) was stirred at 25 °C for 16 h. Then, methoxycarbonyl-(triethylammonio)sulfonyl-azanide (336.5 mg, 1.41 mmol, 1 *eq*) was added at the mixture and the mixture was stirred at 25°C for 16 hr. LC-MS showed that the desired compound was detected. TLC (petroleum ether: ethyl acetate =0:1/I_2) showed new spots were detected. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 23%-53%, 9.5 min). Compound N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (450 mg, 0.98 mmol, 69.9% yield) was obtained as yellow solid.

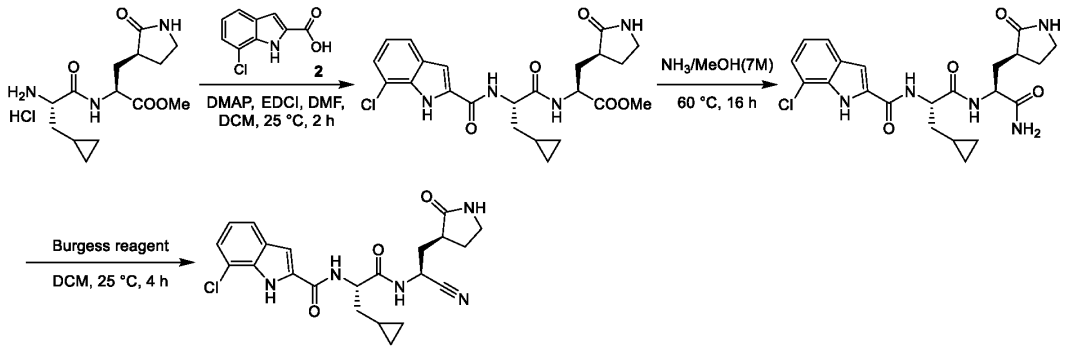
Step 4: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000447] N-[2-[[1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (550.0 mg, 1.22 mmol, 1 *eq*) was purified by SFC(column: DAICEL CHIRALPAK AD(250 mm*30 mm,10 um);mobile phase: [0.1% NH_3H_2O ETOH];B%: 55%-55%, min). Compound N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide, Isomer 1(147.1 mg, 0.25 mmol, 22.1% yield) was obtained as a solid. LCMS： Rt = 0.756 min; for $C_{24}H_{29}N_5O_4$ MS Calcd: 451.22, MS Found:452.1 [M+H^+]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (br s, 1H), 8.90 (br d, *J* = 8.0 Hz, 1H), 8.49 (br d, *J* = 7.4 Hz, 1H), 7.52 (br s, 1H), 7.36 (s, 1H), 7.12 - 7.06 (m, 1H), 7.03 - 6.98 (m, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 5.17 - 4.96 (m, 1H), 4.56 - 4.33 (m, 1H),

3.88 (s, 3H), 3.09 (br s, 2H), 2.33 - 2.19 (m, 2H), 1.88 - 1.76 (m, 3H), 1.70 (br dd, J = 3.8, 8.3 Hz, 1H), 1.57 (br s, 1H), 1.50 - 1.35 (m, 2H), 0.80 (br s, 1H), 0.41 (br d, J = 6.6 Hz, 2H), 0.25 - 0.03 (m, 2H); and

[000448] *N*-[(1*R*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamidem, Isomer 2 (113.1 mg, 0.32mmol, 28.8% yield, 100% purity) was obtained as a solid. LCMS： Rt = 0.761min; for $C_{24}H_{29}N_5O_4$ MS Calcd: 451.22, MS Found:452.0 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.57 (s, 1H), 8.89 (br d, J = 8.0 Hz, 1H), 8.49 (br d, J = 7.6 Hz, 1H), 7.51 (br s, 1H), 7.36 (d, J = 1.6 Hz, 1H), 7.13 - 7.06 (m, 1H), 7.03 - 6.97 (m, 1H), 6.50 (d, J = 7.5 Hz, 1H), 5.08 - 4.99 (m, 1H), 4.52 - 4.42 (m, 1H), 3.88 (s, 3H), 3.08 (br s, 2H), 2.23 - 2.13 (m, 2H), 1.90 - 1.68 (m, 4H), 1.64 - 1.36 (m, 3H), 0.85 - 0.70 (m, 1H), 0.45 - 0.33 (m, 2H), 0.24 - 0.11 (m, 1H), 0.13 - 0.03 (m, 1H).

Example 36. Synthesis of viral protease inhibitor compound 531



Step 1: methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000449] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.68 mmol, 1 *eq*) in DCM (10 mL) and DMF (2.5 mL), was added DMAP (616.30 mg, 5.04 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added 7-chloro-1H-indole-2-carboxylic acid (394.69 mg, 2.02 mmol, 1.2 *eq*) and EDCI (967.04 mg, 5.04 mmol, 3 *eq*). The resulting mixture was stirred at 25 °C for 2 h. Then, the mixture was concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum

ether/Ethyl acetate = 5/1 to 0/1) to give methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (550 mg, 1.16 mmol, 68.87% yield) as a white solid. MS (ESI) *m/z* 475.1 $[M+H]^+$

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide

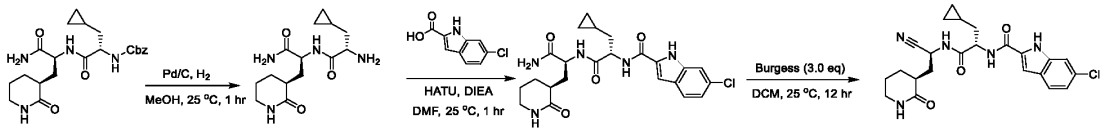
[000450] A mixture of methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.05 mmol, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 66.49 *eq*) was stirred at 60 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (440 mg, 956.68 umol, 90.87% yield) as a solid. MS (ESI) *m/z* 460.3 $[M+H]^+$

Step 3: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000451] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (430 mg, 934.94 umol, 1 *eq*) in DCM (6 mL) was added Burgess reagent (445.61 mg, 1.87 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 30%-60%,8 min) to give 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (180 mg, 407.32 umol, 43.57% yield) as a solid. MS (ESI) *m/z* 442.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ = 11.71 (br s, 1H), 9.01 (d, *J*=7.9 Hz, 1H), 8.72 (d, *J*=7.5 Hz, 1H), 7.71 (s, 1H), 7.63 (dd, *J*=0.7, 7.9 Hz, 1H), 7.34 - 7.25 (m, 2H), 7.07 (t, *J*=7.8 Hz, 1H), 5.00 (q, *J*=7.9 Hz, 1H), 4.58 - 4.49 (m, 1H), 3.13 (quin, *J*=9.2 Hz, 2H), 2.42 - 2.31 (m, 1H), 2.22 -

2.05 (m, 2H), 1.89 - 1.64 (m, 3H), 1.57 - 1.46 (m, 1H), 0.89 - 0.75 (m, 1H), 0.50 - 0.37 (m, 2H), 0.25 - 0.07 (m, 2H).

Example 37. Synthesis of viral protease inhibitor compound 635



Step 1: (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide

[000452] To a solution of benzyl *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (400 mg, 0.92 mmol, 1 *eq*) in MeOH (5 mL) was added Pd (200 mg, 10% purity) and H_2 (0.92 mmol). The mixture was stirred at 25 °C under 15 psi for 1 hr. The mixture was filtered to give the filter liquor. The mixture was concentrated under reduce pressure to give compound (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (274 mg, 0.92 mmol, 99.5% yield) as a solid.

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-1H-indole-2-carboxamide

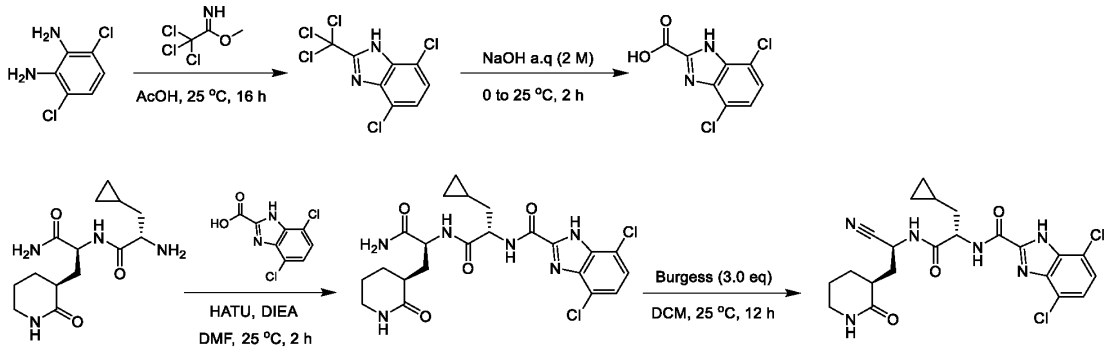
[000453] To a solution of (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (137 mg, 0.46 mmol, 1 *eq*) and 6-chloro-1*H*-indole-2-carboxylic acid (90.4 mg, 0.46 mmol, 1 *eq*) in DMF (2 mL) was added DIPEA (119.4 mg, 0.92 mmol, 0.16 mL, 2 *eq*) and HATU (210.9 mg, 0.55 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed one peak with desired MS was detected. The mixture was concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @ 30 mL/min) to give Compound *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-1*H*-indole-2-carboxamide (200 mg, 89.0%

yield) as a solid. LCMS: Rt = 0.780 min; for $C_{23}H_{28}ClN_5O_4$ MS Calcd.: 473.18; MS Found: 474.1 [M+H$^+$].

Step 3: 6-Chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000454] To a solution of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-1*H*-indole-2-carboxamide (47.5 mg, 0.1 mmol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (71.6 mg, 0.3 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The mixture was concentrated under reduce pressure. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80 * 40 mm * 3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 31%-61%,7.8 min) to give compound 6-chloro-*N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1*H*-indole-2-carboxamide(64.33 mg, 34.7% yield) as a solid. LCMS: Rt = 0.832 min; for $C_{23}H_{26}ClN_5O_3$; MS Calcd.:455.17; MS Found: 456.1 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (br s, 1H), 8.95 (br d, *J*=8.0 Hz, 1H), 8.66 (br d, *J*=7.5 Hz, 1H), 7.66 (d, *J*=8.5 Hz, 1H), 7.53 (br s, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 7.05 (dd, *J*=1.8, 8.5 Hz, 1H), 5.11 - 4.96 (m, 1H), 4.52 - 4.42 (m, 1H), 3.09 (br s, 2H), 2.34 - 2.21 (m, 2H), 1.89 - 1.75 (m, 3H), 1.74 - 1.65 (m, 1H), 1.56 (br s, 1H), 1.51 - 1.29 (m, 2H), 0.79 (br s, 1H), 0.42 (br d, *J*=7.0 Hz, 2H), 0.23 - 0.01 (m, 2H)

Example 38. Synthesis of viral protease inhibitor compound 637



Step 1: 4,7-Dichloro-2-(trichloromethyl)-1H-benzimidazole

[000455] To a solution of 3,6-dichlorobenzene-1,2-diamine (0.3 g, 1.69 mmol, 1 eq) in AcOH (12.57 g, 209.2 mmol, 11.97 mL, 123.8 eq) was added methyl 2,2,2-trichloroacetimidate (313.0 mg, 1.77 mmol, 0.21 mL, 1.05 eq) at 0°C. The mixture was stirred at 25 °C for 16 hr. The resulting mixture was diluted with H_2O (40 mL) and filtered to give 4,7-dichloro-2-(trichloromethyl)-1H-benzo[d]imidazole (300 mg, crude) as a solid.

Step 2: 4,7-Dichloro-1H-benzimidazole-2-carboxylic acid

[000456] To a solution of NaOH (0.8 g, 20.0 mmol, 20.2 eq) in H_2O (10 mL) was added 4,7-dichloro-2-(trichloromethyl)-1H-benzo[d]imidazole (0.3 g, 985.58 umol, 1 eq) at 0 °C. The mixture was stirred at 25°C for 1 hr. The pH of the mixture was adjusted with HCl (2 M) to pH = 2-3 and then the mixture was filtered to give 4,7-dichloro-1H-benzo[d]imidazole-2-carboxylic acid (0.2 g, crude) as a solid.

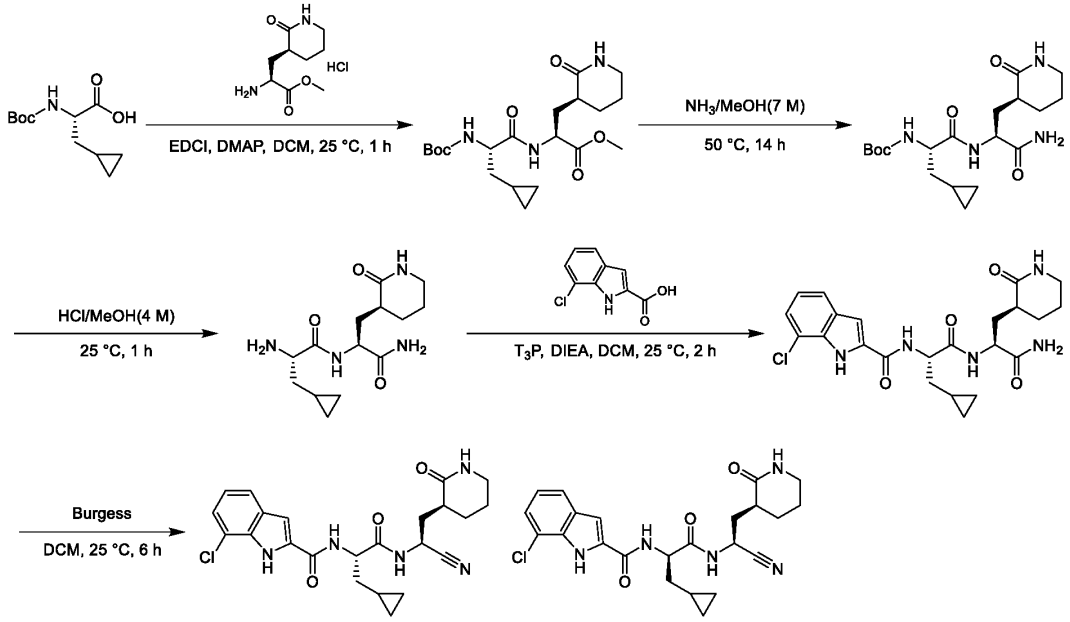
Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,6-dichloro-1H-benzimidazole-2-carboxamide

[000457] To a solution of (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-cyclopropylpropanamide (130 mg, 0.43 mmol, 1 eq) and 4,7-dichloro-1H-benzo[d]imidazole-2-carboxylic acid (101.3 mg, 0.43 mmol, 1.0 eq) in DMF (3 mL) was added HATU (250.1 mg, 0.65 mmol, 1.5 eq) and DIPEA (113.3 mg, 0.87 mmol, 0.15 mL, 2.0 eq). The mixture was stirred at 25 °C for 1 hr. TLC (Dichloromethane: Methanol=10/1) indicated 4,7-dichloro-1H-benzo[d]imidazole-2-carboxylic acid was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 10/1) to give *N*-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,7-dichloro-1H-benzo[d]imidazole-2-carboxamide (0.2 g, 0.39 mmol, 89% yield) as a solid.

Step 4: 4,7-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-benzimidazole-2-carboxamide

[000458] To a solution of *N*-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,7-dichloro-1H-benzo[d]imidazole-2-carboxamide (100.00 mg, 0.19 mmol, 1 eq) in DCM (3.0 mL) was added Burgess Reagent (140.3 mg, 0.58 mmol, 3.0 eq). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40mm*3um; mobile phase: [water (0.05% NH3H2O+10 mM NH4HCO3)-ACN]; B%: 20%-50%, 7.8 min) to give the product (22.11 mg, 22% yield) as a solid. LCMS: Rt = 0.824 min; for $C_{22}H_{24}Cl_2N_6O_3$ MS Calcd.: 490.13; MS Found: 491.1 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.30 (s, 2H), 5.22 - 5.09 (m, 1H), 4.60 (t, *J* = 7.1 Hz, 1H), 3.27 - 3.19 (m, 2H), 2.56 - 2.37 (m, 2H), 2.06 - 1.88 (m, 3H), 1.87 - 1.79 (m, 1H), 1.73 (td, *J* = 7.2, 14.0 Hz, 2H), 1.60 - 1.44 (m, 1H), 0.96 - 0.75 (m, 1H), 0.54 (d, *J* = 6.9 Hz, 2H), 0.21 (dd, *J* = 4.8, 10.4 Hz, 2H).

Example 39. Synthesis of viral protease inhibitor compound 639 and 639A



Step 1: Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000459] To a solution of (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (1.07 g, 4.65 mmol, 1.1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 4.22 mmol, 1 eq, HCl) in DCM (10 mL) was added DMAP (1.55 g, 12.67 mmol, 3 eq) and EDCI (1.62 g, 8.45 mmol, 2 eq). The resulting mixture was stirred at 25 °C for 1 h. Upon completion, the solution was added with H_2O (30 mL), and then extracted with ethyl acetate (30 mL * 3). The combined organic phase was dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 30/1 to 10/1) to give methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl] propanoate (1.2 g, 2.92 mmol, 68.97% yield, 100% purity) was obtained as yellow oil. MS (ESI) *m/z* 412.3 $[M+H]^+$.

Step 2: (2R)-N-(4-(tert-butyl)phenyl)-N-(2-oxo-1-(pyridin-3-yl)-2-((pyridin-4-ylmethyl)amino)ethyl)pyrrolidine-2-carboxamide

[000460] Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (600 mg, 1.46 mmol, 1 eq) in ammonia (7 M, 7.2 mL, 8.30 eq) was stirred at 50 °C for 14 h. Upon completion, the solution was concentrated to give tert-butyl N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl] methyl] ethyl] amino]-1-(cyclopropylmethyl)-2-oxo-ethyl] carbamate (580 mg, crude) as yellow oil. MS (ESI) *m/z* 397.3 $[M+H]^+$.

Step 3: (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide

[000461] Tert-butyl N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (580 mg, 1.46 mmol, 1 eq) in HCl/MeOH (4 M, 10.00 mL, 7.93 eq) was stirred at 25 °C for 1 h. Upon completion, the solution was concentrated to give (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (380 mg, crude) was obtained as yellow oil. MS (ESI) *m/z* 297.2 $[M+H]^+$.

Step 4: (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide

[000462] To a solution of (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (380 mg, 1.28 mmol, 1 eq) in DCM (3 mL) was added 7-chloro-1H-indole-2-carboxylic acid (275.88 mg, 1.41 mmol, 1.1 eq), T_3P (1.22 g, 1.93 mmol, 1.14 mL, 50% purity, 1.5 eq), and DIEA (331.44 mg, 2.56 mmol, 446.68 uL, 2 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the solution was diluted with H_2O (20 mL), extracted with DCM (30 mL * 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (350 mg, 738.47 umol, 57.59% yield, 100% purity) as yellow oil. MS (ESI) *m/z* 474.3 $[M+H]^+$.

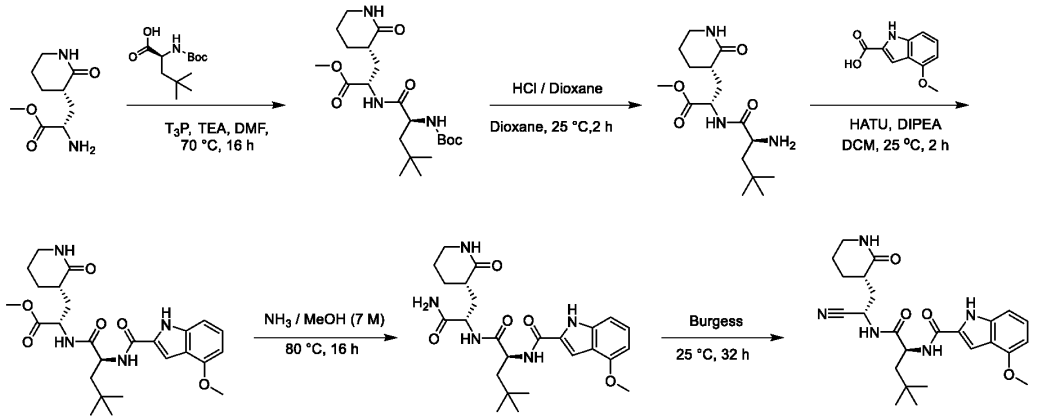
Step 5: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000463] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (350 mg, 738.47 umol, 1 eq) in DCM (4 mL) was added Burgess reagent (527.94 mg, 2.22 mmol, 3 eq), and the solution was stirred at 25 °C for 6 h. Upon completion, DCM was removed using blow dry. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(0.05%NH_3H_2O+10mM $NH4HCO_3$)-ACN];B%: 25%-55%,8min) to afford the product as a solid, which was further separated by SFC (column: DAICEL CHIRALPAK AS(250mm*30mm,10um); mobile phase: [0.1%NH_3H_2O ETOH];B%: 33%-33%,8min) to give:

[000464] 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (250 mg, 530.89 umol, 74.25% yield, 96.82% purity) as a solid. MS (ESI) *m/z* 456.2 $[M+H]^+$. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.58 (d, *J*=7.9 Hz, 1H), 7.35 - 7.20 (m, 2H), 7.06 (t, *J*=7.8 Hz, 1H), 5.22 - 5.05 (m, 1H), 4.57 (t, *J*=7.5 Hz, 1H), 3.27 - 3.14 (m, 2H), 2.61 - 2.34 (m, 2H), 2.09 - 1.61 (m, 6H), 1.59 - 1.43 (m, 1H), 0.98 - 0.76 (m, 1H), 0.55 (dd, *J*=1.3, 8.2 Hz, 2H), 0.31 - 0.09 (m, 2H); and

[0000465] 7-chloro-N-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (45 mg, 98.70 umol, 13.37% yield, 100% purity) as a solid. MS (ESI) *m/z* 456.2 $[M+H]^+$. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.59 (dd, *J*=0.9, 7.9 Hz, 1H), 7.32 - 7.21 (m, 2H), 7.07 (t, J=7.8 Hz, 1H), 5.12 - 5.02 (m, 1H), 4.59 (dd, *J*=6.4, 7.9 Hz, 1H), 3.21 (dd, *J*=4.6, 7.7 Hz, 2H), 2.44 - 2.23 (m, 2H), 2.09 - 1.62 (m, 6H), 1.60 - 1.47 (m, 1H), 0.94 - 0.78 (m, 1H), 0.62 - 0.43 (m, 2H), 0.27 - 0.11 (m, 2H).

Example 40. Synthesis of viral protease inhibitor compound 643



Step 1: Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0000466] T_3P (2.69 g, 4.22 mmol, 2.51 mL, 50% purity, 2 *eq*) was added to a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 2.11 mmol, 1 *eq*, HCl), (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (570.0 mg, 2.32 mmol, 1.1 *eq*) and TEA (855.0 mg, 8.45 mmol, 1.18 mL, 4 *eq*) in DMF (5 mL). The resulting mixture was stirred at 70°C for 16hr. TLC (petroleum ether: ethyl acetate =0:1/PMA) showed new spots were detected. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®;20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ethergradient @30 mL/min). Compound methyl (2S)-2-[[(2S)-2-(tert-

butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (436 mg, 0.99 mmol, 47.2% yield, 97.9% purity) was obtained as a solid.

Step 2: Methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000467] Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (300 mg, 0.70 mmol, 1 *eq*) in HCl/dioxane (4 M, 175.42 uL, 1 *eq*) was stirred at 25°C for 2hr. Compound methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (250 mg, crude, HCl) was obtained as a solid and was used into next step without further purification.

Step 3: Methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000468] A mixture of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (310 mg, 0.85 mmol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (179.1 mg, 0.93 mmol, 1.1 *eq*), HATU (647.8 mg, 1.70 mmol, 2 *eq*) and DIPEA (440.4 mg, 3.41 mmol, 0.60 mL, 4 *eq*) in DCM (4 mL) was stirred at 25°C for 2hr. TLC (petroleum ether/ethyl acetate =0:1/UV 254nm) showed new spots were detected. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ethergradient @ 30mL/min). Compound methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (451 mg, 0.68 mmol, 80.1% yield) was obtained as an oil and confirmed by LC-MS.

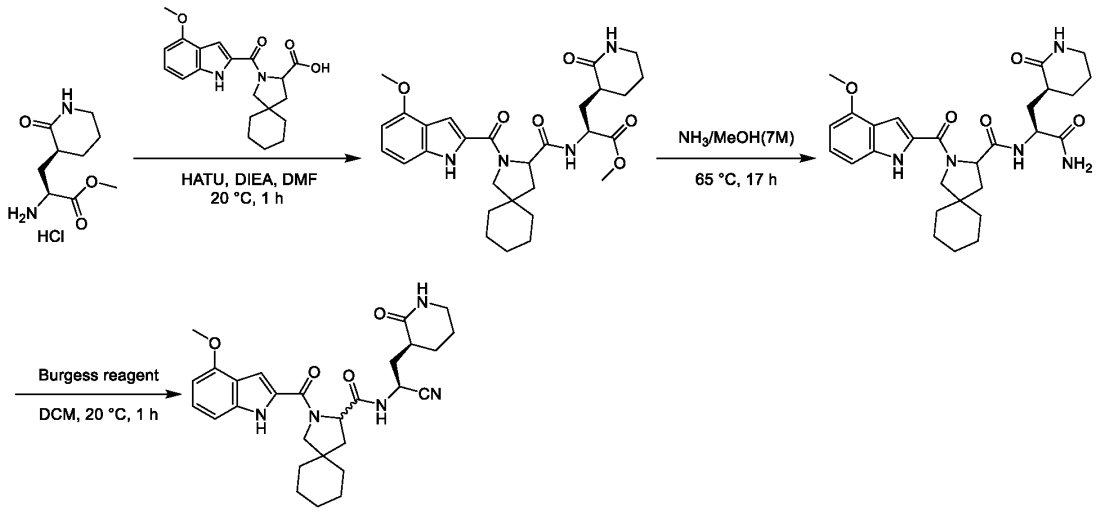
Step 4: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000469] NH_3 (7 M, 11.42 mL, 100 *eq*) was added to a mixture of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (400 mg, 0.79 mmol, 1 *eq*) in MeOH. Then, the mixture was stirred at 80°C for 16hr. TLC (DCM:MeOH=10:1/UV 254nm) showed new spot was detected. The reaction mixture was concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®;12g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/MeOH @30 mL/min). Compound N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (295 mg, 0.60 mmol, 75.1% yield, 98.9% purity) was obtained as a solid.

Step 5: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000470] Methoxycarbonyl-(triethylammonio)sulfonyl-azanide (284.6 mg, 1.19 mmol, 2 *eq*) was added at the mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (290 mg, 0.59 mmol, 1 *eq*) in DCM (3 mL) at 25°C. Then the mixture was stirred at 25°C for 16hr. Then methoxycarbonyl-(triethylammonio)sulfonyl-azanide (142.3 mg, 0.59 mmol, 1 *eq*) was added to the mixture and the mixture was stirred at 25°C for anther 16hr. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water (0.05% ammonia hydroxide v/v)-MeOH];B%: 55%-85%,9.5min). Compound N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (28.1 mg, 59.3 umol, 9.9% yield, 98.7% purity) was obtained as a solid. Rt = 0.832 min; for $C_{25}H_{33}N_5O_4$ MS Calcd.: 467.25, MS Found: 468.2 [$M+H^+$]. ^1H NMR (400MHz, CD_3OD) δ 7.26 - 7.22 (m, 1H), 7.18 - 7.12 (m, 1H), 7.05 - 7.00 (m, 1H), 6.51 (d, J = 7.5 Hz, 1H), 5.08 (dd, J = 6.3, 9.8 Hz, 1H), 4.67 - 4.63 (m, 1H), 3.93 (s, 3H), 3.21 - 3.15 (m, 2H), 2.47 - 2.38 (m, 2H), 1.98 - 1.72 (m, 6H), 1.70 - 1.58 (m, 1H), 1.54 - 1.43 (m, 1H), 1.02 (s, 8H), 1.04 - 1.01 (m, 2H).

Example 41. Synthesis of viral protease inhibitor compound 681



Step 1: (2S)-methyl 2-(2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000471] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 2.11 mmol, 1.1 *eq*, HCl) and 2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (684.45 mg, 1.92 mmol, 1 *eq*) in DMF (15 mL) was added *N,N*-diisopropylethylamine (DIEA) (744.57 mg, 5.76 mmol, 1.00 mL, 3 *eq*) and (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (730.19 mg, 1.92 mmol, 1 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the two batch reaction mixture was quenched by addition H_2O (80 mL), and extracted with ethyl acetate (40 mL * 3). The combined organic layers were washed with brine 40 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get the product methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.35 g, crude) was obtained as white solid. MS (ESI) *m/z* 539.3 $[M+H]^+$.

Step 2: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000472] A solution of methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (650 mg,

1.21 mmol, 1 *eq*) in NH_3/MeOH (7 M, 3.45 mL, 20 *eq*) was stirred at 65 °C for 17 h. Upon completion, the two batch reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.22 g, crude) as colorless oil. MS (ESI) *m/z* 524.3 $[M+H]^+$.

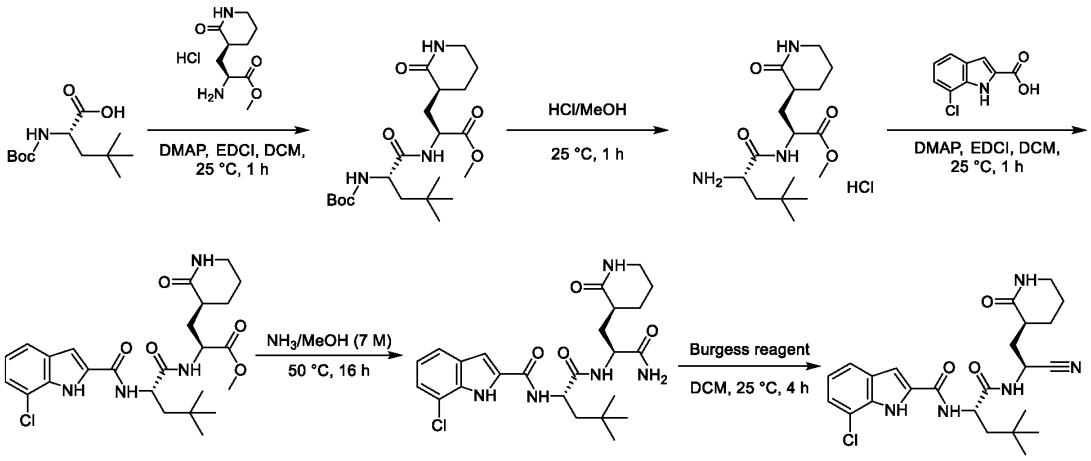
Step 3: N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000473] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.22 g, 2.33 mmol, 1 *eq*) in DCM (20 mL) was added Burgess reagent (1.39 g, 5.82 mmol, 2.5 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by the addition of H_2O (3 mL) and then concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Agela DuraShell C18 250*70mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 43%-63%,20min) to give desired compound (490 mg) as a solid, which was further separated by SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um); mobile phase: [0.1%NH_3H_2O IPA];B%: 58%-58%,10min) to afford the product N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide, Isomer 1 (201.77 mg, 394.36 umol, 16.93% yield) was obtained as white solid. MS (ESI) *m/z* 506.3$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.26 (br s, 1 H) 8.50 - 8.85 (m, 1 H) 7.23 (br s, 1 H) 7.00 - 7.16 (m, 2 H) 6.89 (br s, 1 H) 6.52 (br d, *J* = 7.46 Hz, 1 H) 4.86 - 5.06 (m, 1 H) 4.48 - 4.79 (m, 1 H) 3.80 - 3.98 (m, 4 H) 3.59 (br d, *J* = 4.65 Hz, 1 H) 3.09 (br s, 2 H) 2.15 - 2.31 (m, 3 H) 1.73 - 2.01 (m, 2 H) 1.67 (br dd, *J* = 12.17, 8.62 Hz, 2 H) 1.33 - 1.61 (m, 12 H); and

[000474] N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide, Isomer 2 (200.95 mg, 394.35 umol, 16.93% yield) was obtained as white solid. MS (ESI) *m/z* 506.3$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.27 (br s, 1 H) 8.61 (br d, *J* = 1.22 Hz, 1 H) 7.02 - 7.26 (m, 3 H) 6.91 (br s, 1 H) 6.53 (d, *J* =7.46 Hz, 1 H) 4.91 - 5.06 (m, 1 H) 4.62 (br s, 1 H) 3.82 -

3.98 (m, 4 H) 3.52 - 3.75 (m, 1 H) 3.09 (br s, 2 H) 2.09 - 2.28 (m, 3 H) 1.63 - 1.92 (m, 4 H) 1.33 - 1.62 (m, 12 H).

Example 42. Synthesis of viral protease inhibitor compound 721



Step 1: (S)-methyl2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00475] To a solution of (2*S*)-2-(*tert*-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (2.49 g, 10.14 mmol, 1.2 *eq*) and methyl (2*S*)-2-amino-3-[(3*S*)-2-oxo-3-piperidyl] propanoate (2 g, 8.45 mmol, 1 *eq*, HCl) in DCM (60 mL) was added DMAP (3.10 g, 25.35 mmol, 3 *eq*). Then, EDCI (3.24 g, 16.90 mmol, 2 *eq*) was added, and the resulting mixture was stirred at 25 °C for 1 h. Upon the reaction completement, the mixture was quenched by water (400 mL), extracted with DCM (150 mL * 3), and then was dried by sat. NaCl (50 mL). The resulting solution was concentrated in vacuum and was purified by column (SiO_2, petroleum ether:ethyl acetate = 2:1 to 0:1). The resulting residue was washed with HCl (1 M, 150 mL), extracted with DCM (50 mL * 3), and then the pH of the solution was adjust pH= ~8 with sat. $NaHCO_3$ (30 mL). The resulting mixture was extracted with DCM (100 mL), and then concentrated under vacuum to afford (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-4,4- dimethylpentanamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (3 g, 6.32 mmol, 74.74% yield) as a solid. ^1H NMR (400MHz, $CDCl_3$-*d*) δ ppm 7.61 (d, *J* = 7.0 Hz, 1H), 6.85 - 6.51 (m, 1H), 6.22 (s, 1H), 5.06 - 4.85 (m, 1H), 4.63 - 4.47 (m, 1H), 4.30 - 4.02 (m, 1H), 3.79 - 3.66 (m, 3H), 3.35 - 3.25 (m, 2H), 2.42 -

2.24 (m, 1H), 2.14 - 2.05 (m, 1H), 1.96 - 1.66 (m, 4H), 1.63 - 1.52 (m, 1H), 1.43 (s, 9H), 1.03 - 0.90 (m, 9H).

Step 2: (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000476] A solution of (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl) amino)-4,4-dimethylpentanamido) -3-((*S*)-2-oxopiperidin-3-yl) propanoate (1.5 g, 3.51 mmol, 1 *eq*) in HCl/MeOH (4 M, 20 mL) was stirred at 25 °C for 1 h. Upon the reaction completement, the mixture was concentrated under vacuum to obtain (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin -3-yl)propanoate (1.1 g, crude, HCl) as a solid. ^{1}H NMR (400MHz, D_2O) δ ppm 4.57 (dd, *J* = 4.8, 10.3 Hz, 1H), 3.98 (dd, *J* = 5.2, 7.8 Hz, 1H), 3.78 - 3.65 (m, 3H), 3.29 - 3.14 (m, 2H), 2.75 - 2.33 (m, 1H), 2.24 - 1.47 (m, 8H), 1.04 - 0.86 (m, 9H).

Step 3: (S)-methyl2-((S)-2-(7-chloro-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000477] To a solution of (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin -3-yl)propanoate (550 mg * 2, HCl salt, 1.68 mmol, 1 *eq*) and 7-chloro-1*H*-indole-2-carboxylic acid (394.29 mg, 2.02 mmol, 1.2 *eq*) in DCM (6 mL) was added DMAP (615.66 mg, 5.04 mmol, 3 *eq*). EDCI (644.05 mg, 3.36 mmol, 2 *eq*) was added to the mixture at 25 °C, and the mixture was stirred at 25 °C for 1 h. Upon the reaction completement, the mixture was quenched by water (200 mL), extracted with DCM (70 mL * 3), and then concentrated under vacuum. The resulting residue was purified by column (SiO_2, petroleum ether: ethyl acetate = 1:1 to 0:1), concentrated in vacuum, and then was washed with 1M HCl (100 mL) and extracted with DCM (30 mL * 3). The organic phase was adjusted to pH= ~7 with sat. $NaHCO_3$ (30 mL), and then concentrated in vacuum to obtain (*S*)-methyl 2-((*S*)-2-(7-chloro-1*H*-indole-2-carboxamido)-4,4-dimethylpentanamido) -3-((*S*)-2-oxopiperidin-3-yl)propanoate (650 mg, 1.16 mmol, 40 % yield) as a solid. MS (ESI) *m/z* 505.2 $[M+H]^+$; ^{1}H NMR (400MHz, MeOD-d_4) δ ppm 7.58 (d, *J* = 7.8 Hz, 1H), 7.32 - 7.17 (m, 2H), 7.06 (t, *J* = 7.8 Hz, 1H), 4.73 (dd, *J* = 3.8, 8.6 Hz, 1H), 4.55 (dd, *J* = 4.0, 11.7 Hz, 1H), 3.71 (s, 3H), 3.35 (s, 1H), 3.24 - 3.01 (m, 2H), 2.49 - 2.22 (m, 2H), 2.02 - 1.40 (m, 8H), 1.08 - 0.96 (m, 9H).

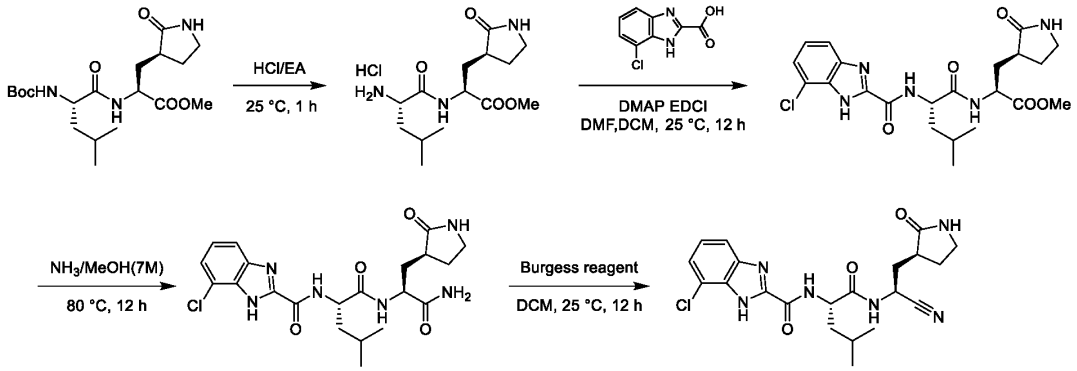
Step 4: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-1H-indole-2-carboxamide

[000478] A solution of (*S*)-methyl 2-((*S*)-2-(7-chloro-1*H*-indole-2-carboxamido)-4,4-dimethylpentanamido) -3-((*S*)-2-oxopiperidin-3-yl)propanoate (650 mg, 1.29 mmol, 1 *eq*) in NH_3/MeOH (7M, 10 mL) was stirred at 50 °C for 16 h. Upon the reaction completement, the mixture was concentrated in vacuum to obtain *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl) amino)-4,4- dimethyl-1-oxopentan-2-yl)-7-chloro-1*H*-indole-2-carboxamide (450 mg, crude) as a light yellow solid. MS (ESI) *m/z* 490.3 $[M+H]^+$

Step 5: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-1H-indole-2-carboxamide

[000479] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl) amino)-4,4- dimethyl-1-oxopentan-2-yl)-7-chloro-1*H*-indole-2-carboxamide (430 mg, 877.56 umol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (627.38 mg, 2.63 mmol, 3 *eq*). The reaction mixture was stirred at 25 °C for 4 h. Upon the reaction completement, the mixture was quenched by water (10 mL), dried with a stream of N_2 and purified by prep-HPLC (column: Kromasil C18 (250*50mm*10 um); mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 35%-65%, 10min) to obtain 7-chloro-*N*-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (205 mg, 424.79 umol, 48.41% yield) as a white solid. MS (ESI) *m/z* 472.2 $[M+H]^+$; 1H NMR (400MHz, DMSO-d_6) δ ppm 11.70 (s, 1H), 9.02 (d, *J* = 8.0 Hz, 1H), 8.71 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.34 - 7.23 (m, 2H), 7.07 (t, *J* = 7.8 Hz, 1H), 5.05 (q, *J* = 8.2 Hz, 1H), 4.63 - 4.54 (m, 1H), 3.07 (s, 2H), 2.30 - 2.18 (m, 2H), 1.88 - 1.32 (m, 7H), 0.95 (s, 9H).

Example 43. Synthesis of viral protease inhibitor compound 133



Step 1: 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid

[000480] A solution of 3-chlorobenzene-1,2-diamine (500 mg, 3.51 mmol, 1 eq) in AcOH (9 mL) was added drop-wise methyl 2,2,2-trichloroethanimidate (619.29 mg, 3.51 mmol, 433.07 uL, 1 eq), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with H_2O 10 mL at 0 °C, and the resultant precipitate was collected. The solid was washed with H_2O (2 * 10 mL) and dried under vacuum to get the product 7-chloro-1H-benzimidazole-2-carboxylic acid (500 mg, crude) was obtained as a solid. MS (ESI) *m/z* 195.1 $[M-H]^+$

Step 2: (S)-methyl 2-((S)-2-amino-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[000481] To a solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 750.98 umol, 1 eq) in EtOAc (2 mL) was added drop-wise HCl/EtOAc (4 M, 20 mL, 106.53 eq), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to get a product methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, crude, HCl) was obtained as a solid.

Step 3: (S)-methyl 2-((S)-2-(7-chloro-1H-benzo[d]imidazole-2-carboxamido)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000482] To a solution of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 744.43 umol, 1.0 eq, HCl) and 7-chloro-

1H-benzimidazole-2-carboxylic acid (243.91 mg, 744.43 umol, 60% purity, 1 eq) in DMF (3 mL) was added EDCI (285.42 mg, 1.49 mmol, 2.0 eq), DMAP (181.89 mg, 1.49 mmol, 2.0 eq). After the addition of DCM (9 mL), the reaction was stirred at 25 °C for 12 h. The reaction mixture was quenched by addition H_2O (40 mL) at 0°C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0/1) to get a product methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-benzimidazole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (220 mg, 327.28 umol, 43.96% yield, 71.1% purity) was obtained as a yellow solid. MS (ESI) *m/z* 478.0 $[M+H]^+$

Step 4: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-7-chloro-1H-benzo[d]imidazole-2-carboxamide

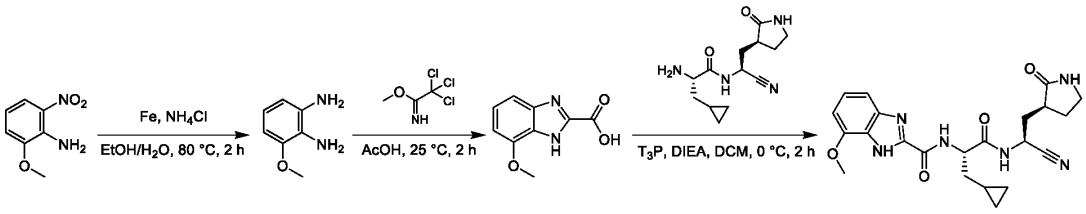
[000483] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-benzimidazole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 418.46 umol, 1 eq) in ammonia (7 M, 20 mL, 334.56 eq) was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure to get a product N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-7-chloro-1H-benzimidazole-2-carboxamide (160 mg, crude) was obtained as a yellow solid. MS (ESI) *m/z* 463.2 $[M+H]^+$

Step 5: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-1H-benzo[d]imidazole-2-carboxamide

[000484] To a solution of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-7-chloro-1H-benzimidazole-2-carboxamide (80 mg, 108.87 umol, 63% purity, 1 eq) in DCM (4 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (129.73 mg, 544.36 umol, 5.0 eq), and then the mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5um;mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 20% - 50%,10 min) and by prep-HPLC (column: Phenomenex Luna C18 75

* 30mm * 3 um;mobile phase: [water(0.2% FA) - ACN]; B%: 10% - 60%, 8min) to afford 7-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-1H-benzimidazole-2-carboxamide (13.28 mg, 29.85 umol, 27.42% yield, 100% purity) as a white solid. MS (ESI) *m/z* 445.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 13.64 (br s, 1H), 8.76 - 9.00 (m, 2H), 7.70 (s, 1H), 7.51 (br d, *J* = 6.2 Hz, 1H), 7.25 - 7.42 (m, 2H), 4.90 - 5.06 (m, 1H), 4.55 (br t, *J* = 7.4 Hz, 1H), 3.05 - 3.18 (m, 2H), 2.33 - 2.42 (m, 1H), 2.05 - 2.23 (m, 2H), 1.54 - 1.90 (m, 5H), 0.92 (br dd, *J* = 8.5, 6.3 Hz, 6H).

Example 44. Synthesis of viral protease inhibitor compound 145



Step 1: 3-methoxybenzene-1,2-diamine:

[000485] To a mixture of 2-methoxy-6-nitro-aniline (1 g, 5.95 mmol, 1.00 mL, 1 *eq*) in EtOH (12 mL) and H_2O (4 mL) was added NH_4Cl (1.59 g, 29.74 mmol, 5 *eq*) in one portion at 25 °C, and then the reaction was heated to 80 °C. Fe (1.66 g, 29.74 mmol, 5 *eq*) was added and stirred for 2 hours at 80 °C. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, and then diluted with H_2O (10 mL) and extracted with ethyl acetate 30 mL (10 mL * 3). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na_2SO_4, and filtered and concentrated under reduced pressure to give 3-methoxybenzene-1,2-diamine (770 mg, 5.02 mmol, 84.34% yield, 90% purity) as a black oil. MS (ESI) *m/z* 139.1 $[M+H]^+$

Step 2: 7-methoxy-1H-benzimidazole-2-carboxylic acid:

[000486] A mixture of 3-methoxybenzene-1,2-diamine (750 mg, 5.43 mmol, 1 *eq*) and methyl 2,2,2-trichloroethanimidate (1.15 g, 6.51 mmol, 803.66 uL, 1.2 *eq*) in AcOH (8 mL) was added in one portion at 25 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was adjusted to neutral by Na_2CO_3 solution, and then diluted with H_2O

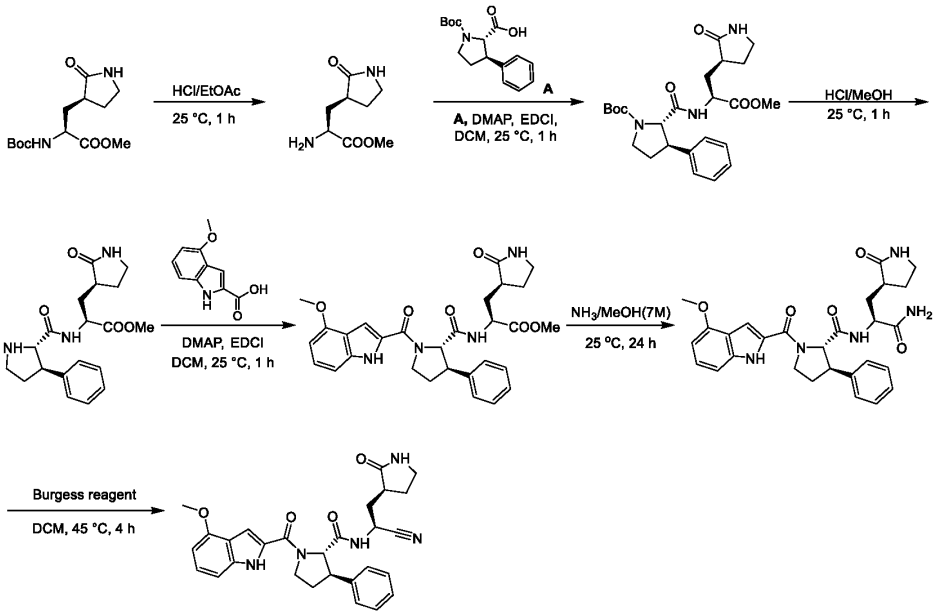
(5 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic layers were washed with brine (10 mL * 1) and concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (TFA condition;) to give 7-methoxy-1H-benzimidazole-2-carboxylic acid (300 mg, 1.56 mmol, 28.76% yield) as a yellow solid. MS (ESI) *m/z* 193.1 $[M+H]^+$ column: Phenomenex luna C18 100*40 mm*5 um; mobile phase: [water(0.1% TFA)-ACN];B%: 20%-55%,8 min

Step 3: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2- oxo-ethyl]-7-methoxy-1H-benzimidazole-2-carboxamide

[000487] To a mixture of 7-methoxy-1H-benzimidazole-2-carboxylic acid (150 mg, 780.55 umol, 1 *eq*) and (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (711.44 mg, 780.55 umol, 29% purity, 1 *eq*) in DCM (3 mL) was added DIEA (302.64 mg, 2.34 mmol, 407.88 uL, 3 *eq*) and T_3P (745.07 mg, 1.17 mmol, 696.33 uL, 50% purity, 1.5 *eq*) in one portion at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with H_2O (5 mL) and then extracted with DCM (5 mL * 3). The combined organic layers were washed with brine (8 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-methoxy-1H-benzimidazole-2-carboxamide (48 mg, 109.47 umol, 14.02% yield) as a white solid. MS (ESI) *m/z* 439.2 $[M+H]^+$. column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 20%-40%, 8 min.

[000488] ^1H NMR (400 MHz, DMSO-d_6) δ = 13.29 (br s, 1H), 9.09 - 8.90 (m, 1H), 8.80 - 8.66 (m, 1H), 7.79 - 7.67 (m, 1H), 7.27 - 7.17 (m, 1H), 7.09 (d, *J*=8.2 Hz, 1H), 6.76 (d, *J*=7.9 Hz, 1H), 5.06 - 4.83 (m, 1H), 4.61 - 4.48 (m, 1H), 3.98 - 3.88 (m, 3H), 3.20 - 3.05 (m, 2H), 2.44 - 2.30 (m, 1H), 2.27 - 2.06 (m, 2H), 1.96 - 1.84 (m, 1H), 1.83 - 1.66 (m, 2H), 1.65 - 1.55 (m, 1H), 0.74 (br s, 1H), 0.40 (br d, *J*=8.2 Hz, 2H), 0.23 - -0.01 (m, 2H)

Example 45. Synthesis of viral protease inhibitor compound 163



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000489] A solution of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl] propanoate (500 mg, 1.75 mmol, 1 *eq*) in HCl/EtOAc (3 mL) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated in vacuum to afford (*S*)-methyl 2-amino-3-((*S*)-2-oxopyrrolidin-3-yl) propanoate (350 mg, crude, HCl) as a yellow gum.

Step 2: (2S,3R)-tert-butyl2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-3-phenylpyrrolidine-1-carboxylate

[000490] To a solution of methyl (*S*)-methyl 2-amino-3-((*S*)-2-oxopyrrolidin-3-yl) propanoate (320 mg, 1.44 mmol, 1 *eq*, HCl) and (2*S*,3*R*)-1-*tert*-butoxycarbonyl-3-phenyl-pyrrolidine-2-carboxylic acid (502.43 mg, 1.72 mmol, 1.2 *eq*) in DCM (15 mL) was added DMAP (526.70 mg, 4.31 mmol, 3 *eq*) and EDCI (1.38 g, 7.19 mmol, 5 *eq*), and then the mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was poured into water (45 mL) and was extracted with DCM (20 mL * 3), then was concentrated in vacuum and was purified by column (SiO_2, PE:EA = 1:1 to 0:1 and then DCM:MeOH = 10:1 to 5:1) to afford (2*S*,3*R*)-*tert-butyl*2-(((*S*)-1-methoxy-1-oxo-3-((*S*)-2- oxopyrrolidin-

3-yl)propan-2-yl)carbamoyl)-3-phenylpyrrolidine-1-carboxylate (500 mg, 544.03 umol, 37.86% yield, 50% purity) as a white solid. MS (ESI) *m/z* 460.3 $[M+H]^+$

Step 3: (S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-((2S,3R)-3-phenylpyrrolidine-2-carboxamido)propanoate

[000491] A solution of (2*S*,3*R*)-*tert-butyl*2-(((*S*)-1-methoxy-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl) carbamoyl)-3-phenylpyrrolidine-1-carboxylate (500 mg, 1.09 mmol, 1 *eq*) in HCl/MeOH (4 M, 5 mL) was stirred at 25 °C for 1 h. Upon reaction completion, the mixture was concentrated in vacuum to afford (*S*)-methyl 3-((*S*)-2-oxopyrrolidin-3-yl)-2-((2*S*,3*R*)-3-phenylpyrrolidine-2-carboxamido) propanoate (340 mg, crude, HCl) as a light yellow solid.

Step 4: (S)-methyl2-((2S,3R)-1-(4-methoxy-1H-indole-2-carbonyl)-3-phenylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000492] To a solution of (*S*)-methyl 3-((*S*)-2-oxopyrrolidin-3-yl)-2-((2*S*,3*R*)-3-phenylpyrrolidine-2-carboxamido) propanoate (200 mg, 278.23 umol, 50% purity, 1 *eq*) and 4-methoxy-1*H*-indole-2-carboxylic acid (63.83 mg, 333.87 umol, 1.2 *eq*) in DCM (5 mL) was added DMAP (101.97 mg, 834.68 umol, 3 *eq*) and EDCI (106.67 mg, 556.45 umol, 2 *eq*), and then the mixture was stirred at 25 °C for 1 h. Upon the reaction completion, the mixture was quenched by water (30 mL) and was extracted with DCM (10 mL * 3). The resultant was concentrated in vacuum and was purified by prep-TLC (SiO_2, ethyl acetate = 1) to afford (*S*)-methyl 2-((2*S*,3*R*)-1-(4-methoxy-1*H*-indole-2-carbonyl)-3-phenylpyrrolidine-2-carboxamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (130 mg, 216.51 umol, 77.82% yield, 88.7% purity) as a white solid. MS (ESI) *m/z* 533.3 $[M+H]^+$

Step 5: (2S,3R)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-3-phenylpyrrolidine-2-carboxamide

[000493] A solution of (*S*)-methyl 2-((2*S*,3*R*)-1-(4-methoxy-1*H*-indole-2-carbonyl)-3-phenylpyrrolidine-2- carboxamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (180 mg, 337.97 umol, 1 *eq*) in NH_3/MeOH (7M, 7.00 mL) was stirred at 25 °C for 24 h. Upon the reaction completion, the mixture was concentrated in vacuum to afford (2*S*,3*R*)-*N*-((*S*)-1-

amino-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl) propan-2-yl)-1-(4-methoxy-1*H*-indole-2-carbonyl)-3-phenylpyrrolidine-2-carboxamide (160 mg, crude) as a white solid. MS (ESI) *m/z* 518.3 $[M+H]^+$

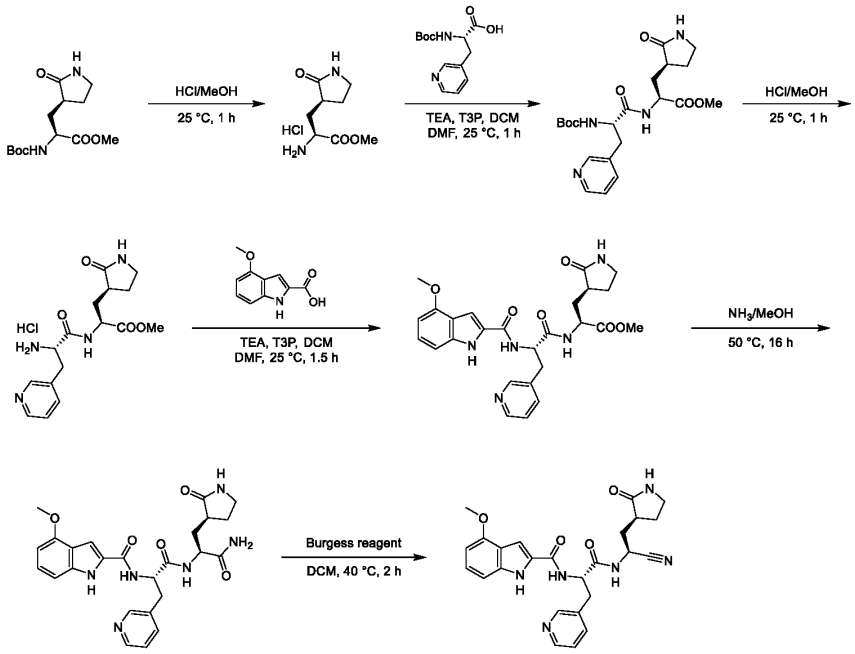
Step 6: (2S,3R)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)-3-phenylpyrrolidine-2-carboxamide

[000494] To a solution of (2*S*,3*R*)-*N*-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4- methoxy-1*H*-indole-2-carbonyl)-3-phenylpyrrolidine-2-carboxamide (160 mg, 309.13 umol, 1 *eq*) in DCM (5 mL) was added Burgess reagent (294.67 mg, 1.24 mmol, 4 *eq*), and then the mixture was stirred at 45 °C for 4 h. Upon the reaction completion, the mixture was quenched by water (3 mL) and was dried by blowing N_2 and was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 25%-55%, 10 min) to afford (2*S*,3*R*)-*N*-((*S*)-1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1*H*-indole-2-carbonyl)-3-phenylpyrrolidine-2-carboxamide (45 mg, 89.18 umol, 28.85% yield, 99% purity) as a white solid. MS (ESI) *m/z* 500.2 $[M+H]^+$.

[000495] ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 11.69 - 11.50 (m, 1H), 9.21 - 8.79 (m, 1H), 7.76 - 7.49 (m, 1H), 7.42 - 7.20 (m, 5H), 7.17 - 6.72 (m, 3H), 6.57 - 6.39 (m, 1H), 5.00 - 4.76 (m, 1H), 4.47 (d, *J* = 6.8 Hz, 1H), 4.17 - 3.72 (m, 5H), 3.55 - 3.38 (m, 1H), 3.17 - 2.77 (m, 2H), 2.46 - 2.34 (m, 2H), 2.30 - 2.01 (m, 3H), 1.79 - 1.31 (m, 2H).

[000496] ^{1}H NMR (400MHz, DMSO-d_6, 273+80K) δ ppm 11.33 (s, 1H), 8.75 (br s, 1H), 7.43 - 7.22 (m, 6H), 7.17 - 7.03 (m, 2H), 6.96 (s, 1H), 6.52 (d, *J* = 7.3 Hz, 1H), 4.99 - 4.87 (m, 1H), 4.63 (s, 1H), 4.08 (s, 2H), 3.90 (s, 3H), 3.50 (q, *J* = 6.8 Hz, 1H), 3.17 - 3.06 (m, 2H), 2.42 (s, 2H), 2.25 - 2.03 (m, 3H), 1.84 - 1.57 (m, 2H).

Example 46. Synthesis of viral protease inhibitor compound 191



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000497] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.75 mmol, 1 *eq*) in HCl/MeOH (4 M, 7 mL, 16.03 *eq*) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, and then the residue was dissolved with DCM (10 mL * 3). The resultant was concentrated under reduced pressure to get afford methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (320 mg, crude) as a white oil. MS (ESI) *m/z* 187.2 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000498] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (320 mg, 1.44 mmol, 1.2 *eq*, HCl) in DCM (4 mL) and DMF (1 mL) added (2S)-2-(tert-butoxycarbonylamino)-3-(3-pyridyl)propanoic acid (318.91 mg, 1.20 mmol, 1 *eq*), TEA (727.10 mg, 7.19 mmol, 1.00 mL, 6 *eq*) and T3P (1.14 g, 1.80 mmol, 1.07 mL, 50% purity, 1.5 *eq*) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a

residue. The residue was purified by silica gel chromatography (SiO_2, DCM:MeOH = 9:1) and TLC (SiO_2, DCM:MeOH = 10:1) to get the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (490 mg, 1.13 mmol, 94.17% yield) as a yellow oil. MS (ESI) *m/z* 435.3 $[M+H]^+$.

Step 3: methyl (2S)-2-[[(2S)-2-amino-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000499] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (450 mg, 1.04 mmol, 1 *eq*) in HCl/MeOH (4 M, 6 mL, 23.17 *eq*) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to get the product methyl (2S)-2-[[(2S)-2-amino-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (340 mg, crude) as white oil. MS (ESI) *m/z* 335.1 $[M+H]^+$.

Step 4: methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000500] A mixture of methyl (2S)-2-[[(2S)-2-amino-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (340 mg, 916.86 umol, 1 *eq*, HCl) in DCM (2 mL) and DMF (2 mL) then added 4-methoxy-1H-indole-2-carboxylic acid (210.35 mg, 1.10 mmol, 1.2 *eq*), TEA (556.66 mg, 5.50 mmol, 765.70 uL, 6 *eq*) and T3P (875.18 mg, 1.38 mmol, 817.93 uL, 50% purity, 1.5 *eq*) was stirred at 25 °C for 1.5 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) and TLC (SiO_2, DCM:MeOH = 10:1) to get the product methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (180 mg, 354.65 umol, 38.68% yield) as yellow solid. MS (ESI) *m/z* 508.2 $[M+H]^+$.

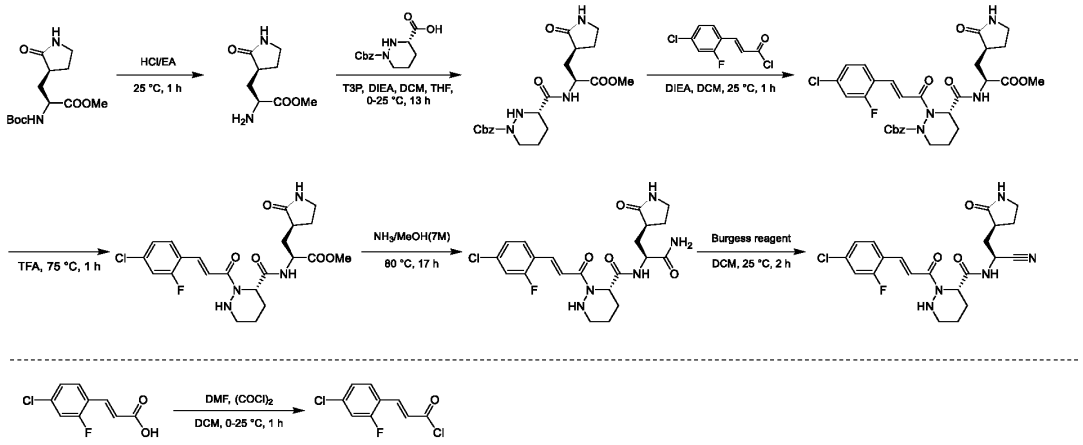
Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-2-oxo-1-(3-pyridylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide

[000501] A mixture of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-(3-pyridyl)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (165 mg, 325.10 umol, 1 *eq*) in NH_3/MeOH (7 M, 5 mL, 107.66 *eq*) was stirred at 50 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-2-oxo-1-(3-pyridylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide (150 mg, crude) as yellow solid. MS (ESI) *m/z* 493.2 $[M+H]^+$.

Step 6: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-2-oxo-1-(3-pyridylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide

[000502] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-2-oxo-1-(3-pyridylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide (126 mg, 255.82 umol, 1 *eq*) in DCM (3 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (243.86 mg, 1.02 mmol, 4 *eq*), and the reaction was stirred at 40 °C for 2 h. Upon completion, the mixture were quenched with water (1 mL) and blow-dried with N_2. The residue was purified by prep-HPLC (column: Waters X bridge BEH C18 100 * 25 mm * 5 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 15% - 45%, 10 min) to afford N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-2-oxo-1-(3-pyridylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide (30.52 mg, 64.32 umol, 25.14% yield, 100% purity) as a white solid. MS (ESI) *m/z* 475.2 $[M+H]^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.50 (d, *J*=1.5 Hz, 1H), 8.41 - 8.34 (m, 1H), 7.80 (br d, *J*=7.9 Hz, 1H), 7.37 (dd, *J*=4.9, 7.8 Hz, 1H), 7.21 (s, 1H), 7.13 (d, *J*=7.7 Hz, 1H), 7.00 (d, *J*=8.2 Hz, 1H), 6.50 (d, *J*=7.7 Hz, 1H), 5.03 (dd, *J*=6.0, 10.0 Hz, 1H), 4.76 (s, 1H), 3.92 (s, 3H), 3.30 - 3.21 (m, 3H), 3.17 (dd, *J*=8.8, 13.9 Hz, 1H), 2.56 (dq, *J*=5.5, 9.3 Hz, 1H), 2.36 - 2.21 (m, 2H), 1.96 - 1.73 (m, 2H).

Example 47. Synthesis of viral protease inhibitor compound 213



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000503] Methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (501 mg, 1.75 mmol, 1 eq) in HCl/EtOAc (4 M, 10.02 mL, 22.91 eq) was stirred at 25 °C for 1 h. Upon completion, the solution was concentrated to remove the HCl/EA. The crude was used to next step directly and without further purification. Methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl] propanoate (300 mg, crude) was obtained as yellow oil.

Step 2: (S)-benzyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)tetrahydropyridazine-1(2H)-carboxylate

[000504] A solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (295.93 mg, 1.59 mmol, 1.4 eq) and (3S)-1-benzyloxycarbonylhexahydropyridazine-3-carboxylic acid (300 mg, 1.14 mmol, 1 eq) in DCM (2 mL)/THF (2 mL) was cooled to 0 °C, and then the T3P (1.08 g, 1.70 mmol, 1.01 mL, 50% purity, 1.5 eq) and DIEA (440.14 mg, 3.41 mmol, 593.18 uL, 3 eq) were added. After stirring at 25 °C for 13 h, the solution was diluted with H_2O (20 mL) and extracted with ethyl acetate (30 mL*3). The combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The crude was used to next step directly and without further purification. Benzyl (3S)-3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl] ethyl] carbamoyl] hexahydropyridazine-1-carboxylate (455 mg, crude) was obtained as yellow oil. MS (ESI) *m/z* 433.1 $[M+H]^+$.

Step 3: (S)-benzyl 2-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)tetrahydropyridazine-1(2H)-carboxylate

[000505] To a solution of benzyl (3S)-3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]hexahydropyridazine-1-carboxylate (200 mg, 462.46 umol, 1 eq) in DCM (2 mL) was added the DIEA (119.54 mg, 924.92 umol, 161.10 uL, 2 eq), (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl chloride (121.56 mg, 554.95 umol, 1.2 eq), and then the solution was stirred at 25 °C for 1 h. Upon completion, the solution was diluted with H_2O (10 mL), extracted with DCM (20 mL*3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1). Benzyl (3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl) prop-2-enoyl]-3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl] ethyl] carbamoyl] hexahydropyridazine-1-carboxylate (160 mg, 248.88 umol, 53.82% yield, 95.67% purity) was obtained as yellow oil. MS (ESI) *m/z* 433.1 $[M+H]^+$.

Step 4: (S)-methyl 2-((S)-2-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)hexahydropyridazine-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000506] Benzyl (3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]hexahydropyridazine-1-carboxylate (160 mg, 260.14 umol, 1 eq) in TFA (5 mL) was stirred at 75 °C for 1 h. Upon completion, the solution was concentrated to remove the TFA, diluted with the solution of $NaHCO_3$, and extracted with ethyl acetate (20 mL*3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give the crude. The crude was used to next step directly and without further purification. Methyl (2S)-2-[[(3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl) prop-2-enoyl] hexahydropyridazine-3-carbonyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propanoate (80 mg, crude) was obtained as yellow solid. MS (ESI) *m/z* 481.0 $[M+H]^+$.

Step 5: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)hexahydropyridazine-3-carboxamide

[000507] Methyl (2S)-2-[[(3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]hexahydropyridazine-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (80 mg, 166.35 umol, 1 eq) in ammonia (7 M, 4.00 mL, 168.32 eq) was stirred at 80 °C for 17 h. Upon completion, the solution was concentrated to remove the MeOH. The crude was used for the next step directly and without further purification. (3S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl] ethyl]-2-[(E)-3-(4-chloro-2-fluoro-phenyl) prop-2-enoyl] hexahydropyridazine-3-carboxamide (75 mg, crude) was obtained as yellow oil. MS (ESI) *m/z* 481.0 $[M+H]^+$.

Step 6: (S)-2-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)hexahydropyridazine-3-carboxamide

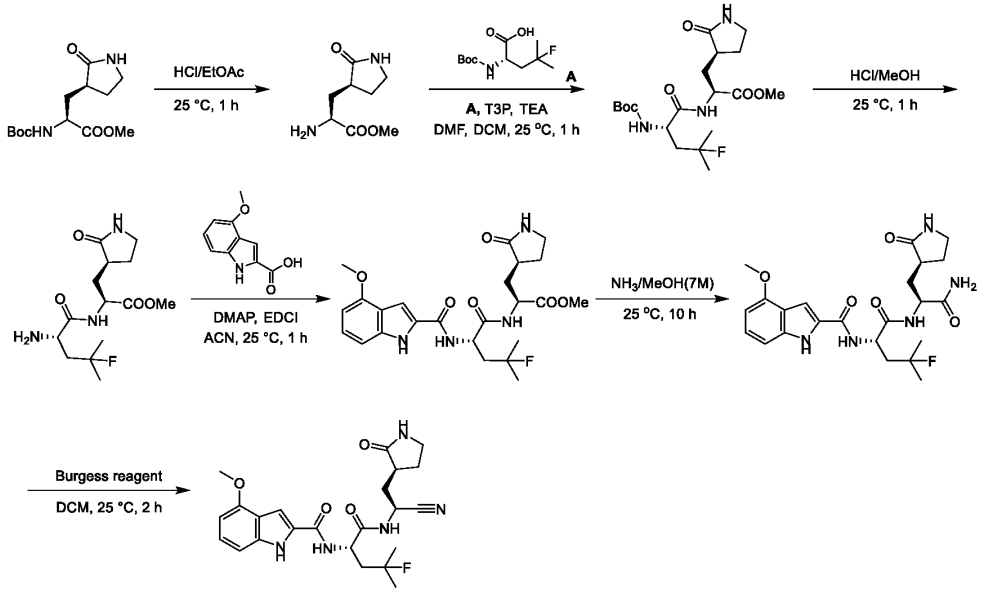
[000508] To a solution of (3S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]hexahydropyridazine-3-carboxamide (75 mg, 160.98 umol, 1 eq) in DCM (0.5 mL) was added the Burgess reagent (76.72 mg, 321.95 umol, 2 eq) and the solution was stirred at 25 °C for 2 h. Upon completion, the solution was concentrated to remove the DCM. The residue was purified by prep-HPLC (neutral condition). Column: Phenomenex Gemini-NX 80*40mm*3um; mobile phase: [water (10mM NH4HCO3)-ACN]; B%: 25%-45%, 8min. (3S)-2-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]hexahydropyridazine-3-carboxamide (20 mg, 44.65 umol, 27.74% yield, 100% purity) was obtained as a white solid. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.79 - 7.60 (m, 3H), 7.32 - 7.22 (m, 2H), 5.17 (dd, *J*=2.2, 6.0 Hz, 1H), 5.07 (dd, *J*=6.4, 9.7 Hz, 1H), 3.38 - 3.32 (m, 2H), 3.12 (br d, *J*=13.7 Hz, 1H), 2.90 - 2.74 (m, 1H), 2.56 (dq, *J*=5.8, 9.0 Hz, 1H), 2.44 - 2.14 (m, 3H), 2.08 - 1.79 (m, 3H), 1.75 - 1.53 (m, 2H). MS (ESI) *m/z* 448.2 $[M+H]^+$.

Step 7: (E)-3-(4-chloro-2-fluorophenyl)acryloyl chloride

[000509] To a solution of (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoic acid (120 mg, 598.22 umol, 1 eq) in DCM (0.5 mL) was added the DMF (437.26 ug, 5.98 umol, 0.46 uL, 0.01 eq), and the reaction was cooled to 0 °C. $(COCl)_2$ (151.86 mg, 1.20 mmol, 104.73 uL, 2 eq) was added and the solution was stirred at 25 °C for 1 h. Upon completion, the solution was concentrated to remove the DCM and give the crude. The

crude was used to next step directly and without furtehr purification. (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl chloride (125 mg, crude) was obtained as white solid.

Example 48. Synthesis of viral protease inhibitor compound 203



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000510] A solution of (*S*)-methyl 2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (600 mg, 2.10 mmol, 1 *eq*) in HCl/EtOAc (20 mL) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated in the vacuum to give a crude product (*S*)-methyl 2-amino-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (530 mg, crude) as yellow solid. MS (ESI) *m/z* 187.1 $[M+H]^+$

Step 2:(S)-methyl2-((S)-2-((tert-butoxycarbonyl)amino)-4-fluoro-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000511] To a solution of methyl (*S*)-methyl 2-amino-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (530 mg, 2.85 mmol, 1 *eq*) in DMF (1 mL) and DCM (10 mL) was added (*S*)-2-((tert-butoxycarbonyl)amino)-4-fluoro-4-methylpentanoic acid (710.44 mg, 2.85 mmol, 1 *eq*), T3P (2.36 g, 3.71 mmol, 2.20 mL, 50% purity, 1.3 *eq*) and TEA (865.17 mg, 8.55 mmol, 1.19 mL, 3 *eq*), and the mixture was stirred at 25 °C for 1 h. Upon

completion, the mixture was quenched by addition H_2O (50 mL) and then extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue and was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1) to give the crude product (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-4-fluoro-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (730 mg, 1.57 mmol, 55.19% yield, 89.95% purity) was yellow oil. MS (ESI) *m/z* 418.2 $[M+H]^+$

Step 3: (S)-methyl2-((S)-2-amino-4-fluoro-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000512] A solution of (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-4-fluoro-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (530.00 mg, 1.27 mmol, 1 *eq*) in HCl/MeOH (20 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction was concentrated in the vacuum to give the crude product (*S*)-methyl 2-((*S*)-2-amino-4-fluoro-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (500 mg, crude) was yellow solid. MS (ESI) *m/z* 318.2 $[M+H]^+$

Step 4: (S)-methyl2-((S)-4-fluoro-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000513] To a solution of (*S*)-methyl 2-((*S*)-2-amino-4-fluoro-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (500.00 mg, 1.58 mmol, 1 *eq*) in ACN (20 mL) was added 4-methoxy-1*H*-indole-2-carboxylic acid (301.21 mg, 1.58 mmol, 1 *eq*), DMAP (384.96 mg, 3.15 mmol, 2 *eq*), EDCI (604.06 mg, 3.15 mmol, 2 *eq*) and the mixture was stirred at 25 °C for 1 h. Upon completion, the residue was poured into H_2O (50 mL) and was extracted with EtOAc (20 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with Na_2SO_4, filtered and concentrated in vacuum and was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1**)** to give product (*S*)-methyl 2-((*S*)-4-fluoro-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (340 mg, 652.80 umol, 41.43% yield, 94.18% purity). MS (ESI) *m/z* 491.2 $[M+H]^+$

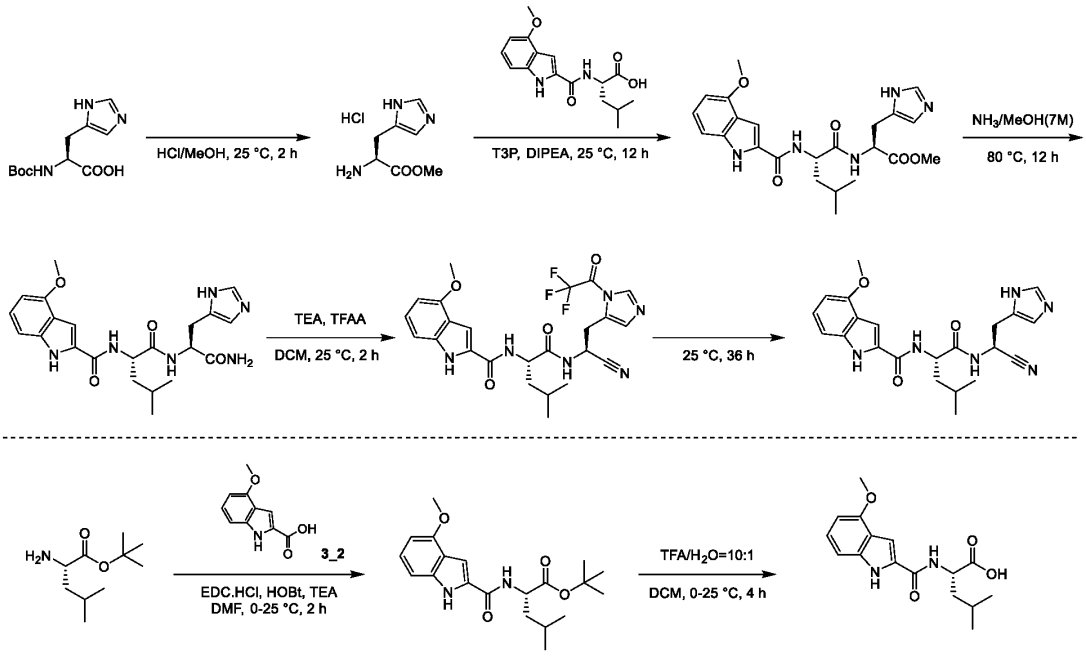
Step5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-fluoro-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000514] A solution of (*S*)-methyl 2-((*S*)-4-fluoro-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (330 mg, 672.75 umol, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 104.05 *eq*) was stirred at 25 °C for 10 h. Upon, completion, the mixture was concentrated in the vacuum, to give crude product N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-fluoro-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (280 mg, crude) as a yellow solid. MS (ESI) *m/z* 476.2 $[M+H]^+$

Step6: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-4-fluoro-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000515] To a solution of N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-fluoro-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (220 mg, 462.66 umol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (1.10 g, 4.63 mmol, 10 *eq*) and the mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated in the vacuum and was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 * 30mm * 3um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 20%-50%,8min) to give product N-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)amino)-4-fluoro-4-methyl-1-oxopentan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (10 mg, 21.86 umol, 4.72% yield, 100% purity). MS (ESI) *m/z* 458.2 $[M+H]^+$ ^1H NMR (400MHz, MeOD-d_4) δ = 7.22 (s, 1H), 7.18 - 7.12 (m, 1H), 7.03 - 7.02 (m, 1H), 6.52 - 6.50 (m, 1H), 5.06 - 5.03 (m, 1H), 4.74 - 4.72 (m, 1H), 3.93 (s, 3H), 3.29 - 3.19 (m, 2H), 2.32 - 2.31 (m, 1H), 2.36 - 2.25 (m, 3H), 2.24 - 2.14 (m, 1H), 1.93 - 1.76 (m, 2H), 1.48 - 1.46 (m, 3H), 1.43 - 1.41 (m, 3H)

Example 49. Synthesis of viral protease inhibitor compound 223



Step 1: methyl (2S)-2-amino-3-(1H-imidazol-5-yl) propanoate

[000516] To the solution of (2S)-2-(tert-butoxycarbonylamino)-3-(1H-imidazol-5-yl)propanoic acid (0.5 g, 1.96 mmol, 1 *eq*) in MeOH (0.6 mL) was added HCl/MeOH (4 M, 4.90 mL, 10 *eq*) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to afford methyl (2S)-2-amino-3-(1H-imidazol-5-yl) propanoate (400 mg, crude, HCl) as white solid, which was used directly next step. MS (ESI) *m/z* 170.1 $[M+H]^+$

Step 2: methyl (2S)-3-(1H-imidazol-5-yl)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino] -4-methyl-pentanoyl]amino]propanoate

[000517] To a mixture of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (741.86 mg, 1.77 mmol, 1 *eq*, TFA) and methyl (2S)-2-amino-3-(1H-imidazol-5-yl)propanoate (0.3 g, 1.77 mmol, 1 *eq*, HCl), DIPEA (1.15 g, 8.87 mmol, 1.54 mL, 5 *eq*) in THF (0.3 mL) and DCM (0.3 mL) was added T3P (1.69 g, 2.66 mmol, 1.58 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was washed with

brine (3 mL * 3) and dried over anhydrous sodium sulfate and concentrated to get the crude product. Methyl (2S)-3-(1H-imidazol-5-yl)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino] -4-methyl-pentanoyl]amino]propanoate (300 mg, crude) was obtained as the white solid and used directly next step. MS (ESI) *m/z* 456.2 $[M+H]^{+}$. 1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.48 (s, 1 H), 7.27 (s, 1 H), 7.11 - 7.18 (m, 1 H), 7.02 (d, *J* = 8.16 Hz, 1 H), 6.85 (s, 1 H), 6.51 (d, *J* = 7.72 Hz, 1 H), 4.60 - 4.71 (m, 2 H), 3.93 (s, 3 H), 3.68 (s, 3 H), 3.00 - 3.17 (m, 3 H), 1.62 - 1.78 (m, 3 H), 0.97 (dd, *J* = 13.78, 6.06 Hz, 6 H)

Step 3: N-[(1S)-1-[[(1S)-2-amino- 1-(1H-imidazol-5-ylmethyl)-2-oxo-ethyl]carbamoyl]-3-methyl-butyl] -4-methoxy-1H-indole-2-carboxamide

[000518] To methyl (2S)-3-(1H-imidazol-5-yl)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-met hyl-pentanoyl]amino]propanoate (200 mg, 439.07 umol, 1 *eq*) was added NH_3/MeOH (7 M, 11.76 mL, 187.56 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C and stirred for 12 h. The reaction mixture was cooled to 25 °C and concentrated to get the crude product. N-[(1S)-1-[[(1S)-2-amino-1-(1H-imidazol-5-ylmethyl)-2-oxo-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (170 mg, 378.83 umol, 86.28% yield, 98.16% purity) was obtained as the light yellow solid and used directly next step. MS (ESI) *m/z* 441.2 $[M+H]^{+}$

Step 4: N-[(1S)-1-[[(1S)-1-cyano-2-(1H-imidazol-5-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy- 1H-indole-2-carboxamide

[000519] To a mixture of N-[(1S)-1-[[(1S)-2-amino-1-(1H-imidazol-5-ylmethyl)-2-oxo-ethyl]carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (140 mg, 317.82 umol, 1 *eq*) in DCM (2 mL) was added TFAA (133.51 mg, 635.65 umol, 88.41 uL, 2 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to get the crude product, which turned into N-[(1S)-1-[[(1S)-1-cyano-2-(1H-imidazol-5-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide after 36 h in storage. The residue was purified by prep-HPLC to afford N-[(1S)-1-[[(1S)-1-cyano-2-(1H-imidazol-5-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (23.89 mg, 56.31 umol, 17.72% yield, 99.581% purity) as a white solid. MS (ESI) *m/z* 423.2 $[M+H]^{+}$

[000520] Prep-HPLC condition: column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-55%,10min; ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.58 (s, 1 H), 7.30 (s, 1 H), 7.12 - 7.21 (m, 1 H), 6.99 - 7.09 (m, 2 H), 6.52 (d, J = 7.72 Hz, 1 H), 5.05 (t, J = 7.06 Hz, 1 H), 4.61 (br dd, J = 9.70, 4.85 Hz, 1 H), 3.94 (s, 3 H), 3.06 - 3.21 (m, 2 H), 1.60 - 1.83 (m, 3 H), 0.99 (dd, J = 13.89, 6.17 Hz, 6 H)

Step 5: tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate

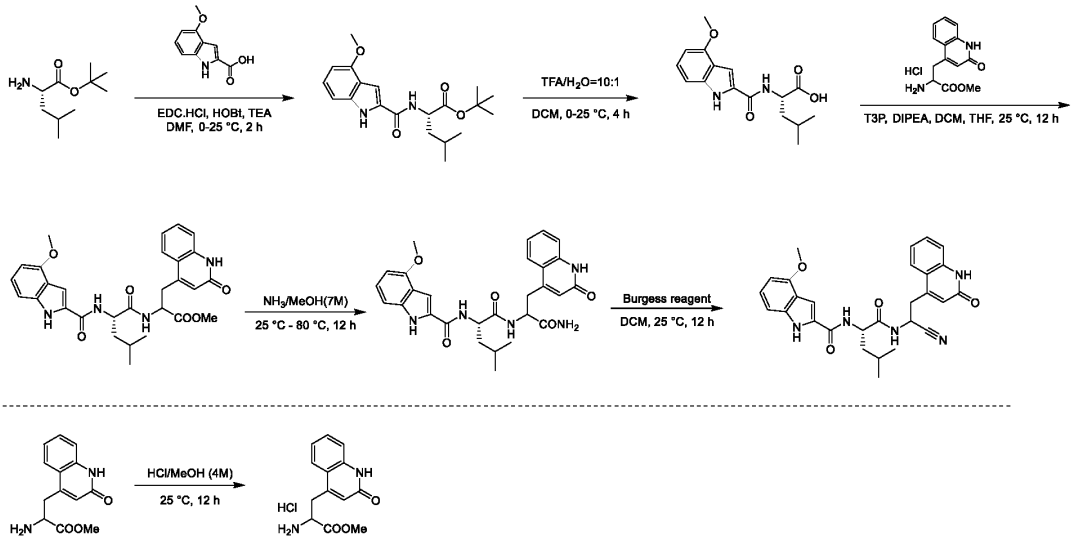
[000521] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (5 g, 26.15 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (5.88 g, 31.38 mmol, 1.2 *eq*, HCl), EDCI (6.52 g, 34.00 mmol, 1.3 *eq*), HOBt (4.59 g, 34.00 mmol, 1.3 *eq*) in DMF (30 mL) was added TEA (7.94 g, 78.46 mmol, 10.92 mL, 3 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was added water (90 mL) and extracted with ethyl acetate (25 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (25 mL) and 5% aqueous solution of sodium bicarbonate (25 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the product. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 30:1 to 10:1). Tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate (5.93 g, 16.45 mmol, 62.91% yield) was obtained as light yellow solid. MS (ESI) *m/z* 361.2 $[M+H]^+$ ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.25 (br s, 1 H), 7.10 - 7.16 (m, 1 H), 6.93 - 7.00 (m, 2 H), 6.56 (br d, J = 8.31 Hz, 1 H), 6.44 (d, J = 7.70 Hz, 1 H), 4.66 (td, J = 8.50, 5.14 Hz, 1 H), 3.88 (s, 3 H), 1.62 - 1.75 (m, 2 H), 1.57 - 1.62 (m, 1 H), 1.42 (s, 9 H), 0.92 (dd, J = 6.17, 3.85 Hz, 6 H).

Step 6: (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid

[000522] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (2.00 g, 5.55 mmol, 1 *eq*) in DCM (8 mL) was added TFA (10.27 g, 90.04 mmol, 6.67 mL, 16.23 *eq*) and H_2O (666.67 mg, 37.01 mmol, 666.67 uL, 6.67 *eq*) in one portion at0 °C under N_2. The mixture was stirred at 25 °C and stirred for 4 h. The reaction mixture was concentrated to get the crude product. (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (2.24 g, 5.35 mmol, 96.50% yield,

TFA) was obtained as the yellow solid and used directly next step. MS (ESI) *m/z* 305.1 $[M+H]^+$

Example 50. Synthesis of viral protease inhibitor compound 237



Step 1: tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate

[000523] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (5 g, 26.15 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (5.88 g, 31.38 mmol, 1.2 *eq*, HCl), EDCI (6.52 g, 34.00 mmol, 1.3 *eq*), HOBt (4.59 g, 34.00 mmol, 1.3 *eq*) in DMF (30 mL) was added TEA (7.94 g, 78.46 mmol, 10.92 mL, 3 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was added water (90 mL) and extracted with ethyl acetate (25 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (25 mL) and 5% aqueous solution of sodium bicarbonate (25 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the product. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 30:1 to 10:1). Tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate (5.93 g, 16.45 mmol, 62.91% yield) was obtained as light yellow solid. MS (ESI) *m/z* 361.2 $[M+H]^+$

[000524] ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.25 (br s, 1 H), 7.10 - 7.16 (m, 1 H), 6.93 - 7.00 (m, 2 H), 6.56 (br d, *J* = 8.31 Hz, 1 H), 6.44 (d, *J* = 7.70 Hz, 1 H), 4.66

(td, J = 8.50, 5.14 Hz, 1 H), 3.88 (s, 3 H), 1.62 - 1.75 (m, 2 H), 1.57 - 1.62 (m, 1 H), 1.42 (s, 9 H), 0.92 (dd, J = 6.17, 3.85 Hz, 6 H).

Step 2: (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid

[000525] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (2.00 g, 5.55 mmol, 1 *eq*) in DCM (8 mL) was added TFA (10.27 g, 90.04 mmol, 6.67 mL, 16.23 *eq*) and H_2O (666.67 mg, 37.01 mmol, 666.67 uL, 6.67 *eq*) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C and stirred for 4 h. The reaction mixture was concentrated to afford (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (2.24 g, 5.35 mmol, 96.50% yield, TFA) as the yellow solid, which was used directly next step. MS (ESI) *m/z* 305.1 $[M+H]^+$

Step 3: methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3- (2-oxo-1H-quinolin-4-yl)propanoate

[000526] To a mixture of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (568.23 mg, 1.36 mmol, 1.2 *eq*, TFA) and methyl 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoate (320 mg, 1.13 mmol, 1 *eq*, HCl), DIPEA (731.40 mg, 5.66 mmol, 985.72 uL, 5 *eq*) in THF (1 mL) and DCM (1 mL) was added T3P (1.08 g, 1.70 mmol, 1.01 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added with saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was concentrated to get the crude product. The residue was purified by prep-HPLC. Methyl 2-[[(2S)-2-[(4-methoxy -1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-(2-oxo-1H-quinolin-4-yl)propanoate (0.2 g, 375.53 umol, 33.18% yield) was obtained as the white solid. MS (ESI) *m/z* 533.2 $[M+H]^+$

[000527] Prep-HPLC condition: column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min

Step 4: N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-1H-quinolin-4-yl)methyl]ethyl]carbamoyl]-3-methyl- butyl]-4-methoxy-1H-indole-2-carboxamide

[000528] To a mixture of methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl] amino]-3-(2-oxo-1H-quinolin-4-yl)propanoate (200.00 mg, 375.53 umol, 1 *eq*) was added NH_3/MeOH (7 M, 10.00 mL, 186.41 *eq*) in one portion at 25 °C

under N_2. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to 25 °C and concentrated to afford N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-1H-quinolin-4-yl)methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (180 mg, 326.21 umol, 86.87% yield, 93.8% purity) as the light yellow solid and used directly next step. MS (ESI) *m/z* 518.2 $[M+H]^+$

Step 5: N-[(1S)-1-[[1-cyano-2-(2-oxo-1H-quinolin-4-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy- 1H-indole-2-carboxamide

[000529] To a mixture of N-[(1S)-1-[[2-amino-2-oxo-1-[(2-oxo-1H-quinolin-4-yl)methyl]ethyl]carbamoyl]-3- methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (90 mg, 173.89 umol, 1 *eq*) in DCM (5 mL) was added Burgess reagent (207.19 mg, 869.44 umol, 5 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated and purified by prep-HPLC. N-[(1S)-1-[[1-cyano-2-(2-oxo-1H-quinolin-4-yl)ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (20.74 mg, 41.13 umol, 23.66% yield, 99.079% purity) was obtained as the white solid. MS (ESI) *m/z* 500.2 $[M+H]^+$

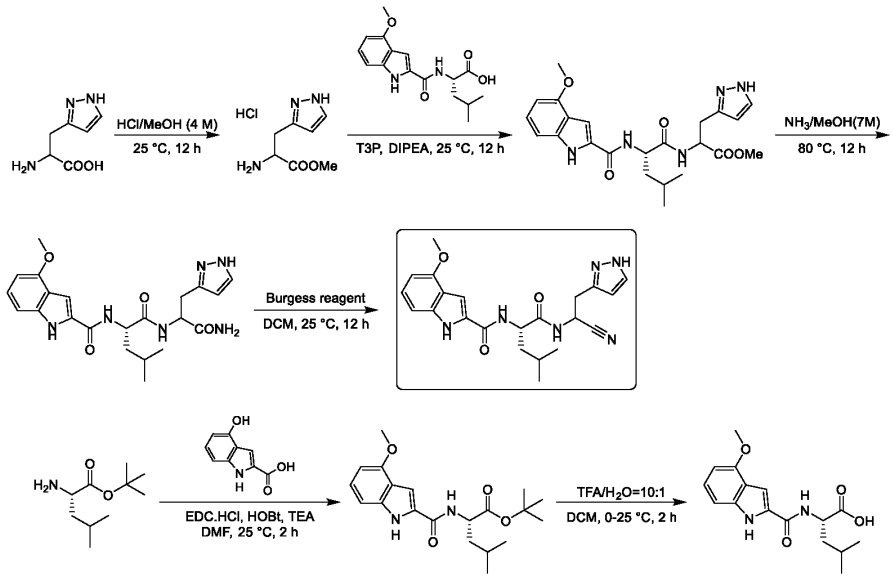
[000530] Prep-HPLC condition: column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-65%,10min

[000531] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.93 (br d, *J* = 8.16 Hz, 1 H), 7.50 - 7.58 (m, 1 H), 7.28 - 7.40 (m, 2 H), 7.26 (dd, *J* = 11.47, 0.66 Hz, 1 H), 7.11 - 7.19 (m, 1 H), 7.04 (dd, *J* = 8.27, 4.08 Hz, 1 H), 6.59 - 6.70 (m, 1 H), 6.46 - 6.56 (m, 1 H), 5.24 - 5.34 (m, 1 H), 4.53 (td, *J* = 10.31, 5.18 Hz, 1 H), 3.93 (d, *J* = 4.41 Hz, 3 H), 3.40 - 3.59 (m, 3 H), 1.72 (ddd, *J* = 15.16, 9.87, 5.18 Hz, 1 H), 1.53 - 1.66 (m, 2 H), 1.40 - 1.50 (m, 1 H), 0.87 - 1.01 (m, 5 H)

Step 6: methyl 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoate

[000532] To 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoic acid (400 mg, 1.72 mmol, 1 *eq*) was added HCl/MeOH (4 M, 4.31 mL, 10 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 1 h. The reaction mixture was concentrated to get the product. Methyl 2-amino-3-(2-oxo-1H-quinolin-4-yl)propanoate (370 mg, crude, HCl) was obtained as the white solid and used directly next step.

Example 51. Synthesis of viral protease inhibitor compound 241



Step 1: methyl 2-amino-3-(1H-pyrazol-3-yl)propanoate

[000533] To 2-amino-3-(1H-pyrazol-3-yl)propanoic acid (0.5 g, 2.19 mmol, 1 *eq*, 2HCl) was added HCl/MeOH (4 M, 17.01 mL, 31.03 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to get the crude product. Methyl 2-amino-3-(1H-pyrazol-3-yl)propanoate (530 mg, crude, 2HCl) was obtained as the yellow solid and used directly next step. MS (ESI) *m/z* 170.1 $[M+H]^+$

Step 2: methyl 2-[[(2S)-2- [(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3- (1H-pyrazol-3-yl)propanoate

[000534] To a mixture of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (377.12 mg, 1.24 mmol, 1 *eq*) and methyl 2-amino-3-(1H-pyrazol-3-yl)propanoate (300 mg, 1.24 mmol, 1 *eq*, 2HCl), DIPEA (800.75 mg, 6.20 mmol, 1.08 mL, 5 *eq*) in THF (0.9 mL) and DCM (0.9 mL) was added T3P (1.18 g, 1.86 mmol, 1.11 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C and stirred for 12 h. The reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was concentrated to get the crude product. The residue was purified by pre-HPLC. Methyl 2-[[(2S)-2- [(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-(1H-

pyrazol-3-yl)propanoate (130 mg, 285.40 umol, 23.03% yield) was obtained as the white solid. MS (ESI) *m/z* 456.2 $[M+H]^+$

[000535] Prep-HPLC condition: column: Phenomenex Gemini-NX 80*40mm*3um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-45%,8min

Step 3: N-[(1S)-1-[[2-amino-2-oxo-1-(1H-pyrazol-3-ylmethyl)ethyl]carbamoyl]-3-methyl-butyl]-4- methoxy-1H-indole-2-carboxamide

[000536] To a mixture of methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl] amino]-3-(1H-pyrazol-3-yl)propanoate (100 mg, 219.54 umol, 1 *eq*) was added NH_3/MeOH (7 M, 3.33 mL, 106.28 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to 25 °C and concentrated to get the product. N-[(1S)-1-[[2-amino -2-oxo-1-(1H-pyrazol-3-ylmethyl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (95 mg, crude) was obtained as the light yellow solid and used directly next step. MS (ESI) *m/z* 441.2 $[M+H]^+$

Step 4: N-[(1S)-1-[[1-cyano-2-(1H-pyrazol-3-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H- indole-2-carboxamide

[000537] To a mixture of N-[(1S)-1-[[2-amino-2-oxo-1-(1H-pyrazol-3-ylmethyl)ethyl]carbamoyl]-3-methyl- butyl]-4-methoxy-1H-indole-2-carboxamide (95 mg, 215.67 umol, 1 *eq*) TEA (43.65 mg, 431.33 umol, 60.04 uL, 2 *eq*) in DCM (0.1 mL) was added TFAA (90.59 mg, 431.33 umol, 60.00 uL, 2 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to get the crude product. The crude product was purified by pre-HPLC. N-[(1S)-1-[[1-cyano-2-(1H- pyrazol-3-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (23.35 mg, 54.93 umol, 25.47% yield, 99.384% purity) was obtained as the white solid MS (ESI) *m/z* 423.2 $[M+H]^+$

[000538] Prep-HPLC condition: column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 25%-55%,8min

[000539] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.55 (br d, *J* = 11.25 Hz, 1 H), 7.30 (s, 1 H), 7.13 - 7.22 (m, 1 H), 7.05 (d, J=7.95 Hz, 1 H), 6.54 (d, *J* = 7.70 Hz, 1 H),

6.31 (dd, *J* = 10.58, 2.14 Hz, 1 H), 5.04 - 5.17 (m, 1 H), 4.56 - 4.64 (m, 1 H), 3.95 (s, 3 H), 3.13 - 3.30 (m, 2 H), 1.52 - 1.83 (m, 3 H), 0.90 - 1.08 (m, 6 H)

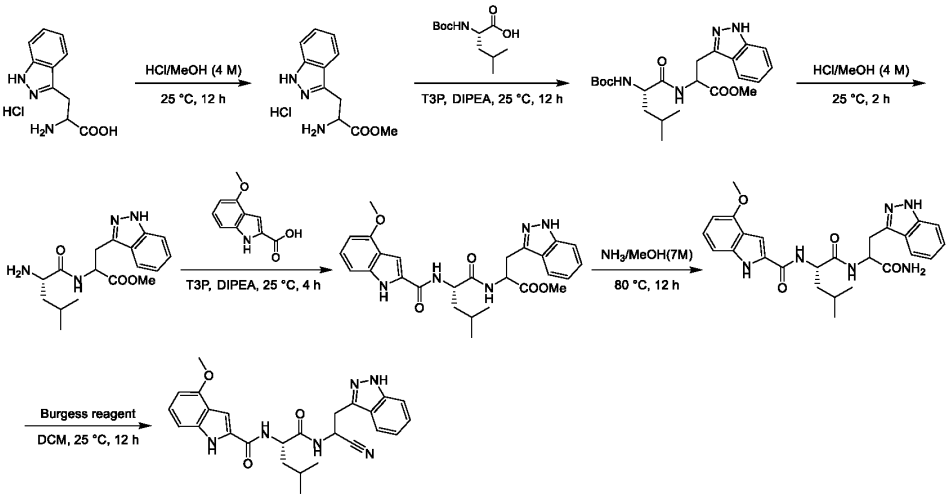
Step 6: (S)-tert-butyl 2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoate

[000540] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (15 g, 78.46 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (21.07 g, 94.15 mmol, 1.2 *eq*, HCl) in DMF (150 mL) was added EDCI (19.55 g, 102.00 mmol, 1.3 *eq*), HOBt (13.78 g, 102.00 mmol, 1.3 *eq*), TEA (23.82 g, 235.38 mmol, 32.76 mL, 3 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was added water (450 mL) and extracted with ethyl acetate (250 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (300 mL) and 5% aqueous solution of sodium bicarbonate (300 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the product. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate=30:1 to 10:1). tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate (24 g, 66.58 mmol, 84.87% yield) was obtained as light yellow solid. MS (ESI) *m/z* 361.2 $[M+H]^+$

Step 7: (S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoic acid

[000541] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (10 g, 27.74 mmol, 1 *eq*) in DCM (30 mL) was added TFA (61.60 g, 540.26 mmol, 40 mL, 19.47 *eq*) and H_2O (4.00 g, 221.98 mmol, 4.00 mL, 8.00 *eq*) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was concentrated to get the crude product. The crude product was purified by petroleum ether:Ethyl acetate = 10:1(20 mL) and filtered to get the product. (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (6 g, 19.22 mmol, 69.27% yield, 97.48% purity) was obtained as the light yellow solid. MS (ESI) *m/z* 305.1 $[M+H]^+$

Example 52. Synthesis of viral protease inhibitor compound 245



Step 1: methyl 2-amino-3-(1H-indazol-3-yl)propanoate

[00542] To a mixture of 2-amino-3-(1H-indazol-3-yl) propanoic acid (200 mg, 827.56 umol, 1 *eq*, HCl) was added HCl/MeOH (4 M, 2 mL, 9.67 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to get the crude product. Methyl 2-amino-3-(1H-indazol -3-yl) propanoate (200 mg, crude, HCl) was obtained as the light yellow solid and used directly next step. MS (ESI) *m/z* 220.1 $[M+H]^+$

Step 2: methyl 2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-(1H-indazol-3-yl) propanoate

[00543] To a mixture of methyl 2-amino-3-(1H-indazol-3-yl)propanoate (150 mg, 586.62 umol, 1 *eq*, HCl) and (2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoic acid (203.52 mg, 879.94 umol, 1.5 *eq*), DIPEA (379.09 mg, 2.93 mmol, 510.90 uL, 5 *eq*) in DCM (1.5 mL) and THF (1.5 mL) was added T3P (559.96 mg, 879.94 umol, 523.33 uL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added with saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2). The organic phase was concentrated to afford methyl 2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino] -3-(1H-indazol-3-yl)propanoate (180 mg, crude) as a light yellow solid. MS (ESI) *m/z* 433.2 $[M+H]^+$

Step 3: methyl 2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-(1H-indazol-3-yl)propanoate

[00544] To a mixture of methyl 2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3- (1H-indazol-3-yl)propanoate (180 mg, 416.17 umol, 1 *eq*) was

added HCl/MeOH (4 M, 5.14 mL, 49.43 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to afford methyl 2-[[(2S)-2-amino-4-methyl-pentanoyl] amino]-3-(1H-indazol-3-yl) propanoate (160 mg, crude, HCl) as light yellow oil and used directly next step. MS (ESI) *m/z* 333.2 $[M+H]^+$

Step 4: methyl 3-(1H-indazol-3-yl)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoyl]amino]propanoate

[000545] To a mixture of methyl 2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-(1H-indazol-3-yl) propanoate (160 mg, 433.77 umol, 1 *eq*, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (99.52 mg, 520.53 umol, 1.2 *eq*), DIPEA (280.31 mg, 2.17 mmol, 377.78 uL, 5 *eq*) in DCM (1 mL) and THF (1 mL) was added T3P (414.05 mg, 650.66 umol, 386.97 uL, 50% purity, 1.5 *eq*) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C for 4 h. The reaction mixture was added with saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2). The organic phase was concentrated to get the crude product. The residue was purified by pre-HPLC. Methyl 3-(1H-indazol-3-yl) -2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino] -4-methyl-pentanoyl] amino]propanoate (80 mg, crude) was obtained as the light yellow solid. MS (ESI) *m/z* 506.2 $[M+H]^+$

[000546] Prep-HPLC condition: column: Phenomenex Gemini-NX 80*40mm*3um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-65%,8min

Step 5: N-[(1S)-1-[[1-(1H-indazol-3-ylmethyl)-2-nitroso-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy -1H-indole-2-carboxamide

[000547] To a mixture of methyl 3-(1H-indazol-3-yl)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino] -4-methyl-pentanoyl]amino]propanoate (80 mg, 158.24 umol, 1 *eq*) was added NH_3/MeOH (7 M, 1 mL, 44.24 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to 25 °C and concentrated. N-[(1S)-1-[[1-(1H-indazol-3-ylmethyl)-2-nitroso-ethyl]carbamoyl]-3-methyl -butyl]-4-methoxy-1H-indole-2-carboxamide (75 mg, crude) was obtained as light yellow solid and used directly next step. MS (ESI) *m/z* 491.2 $[M+H]^+$

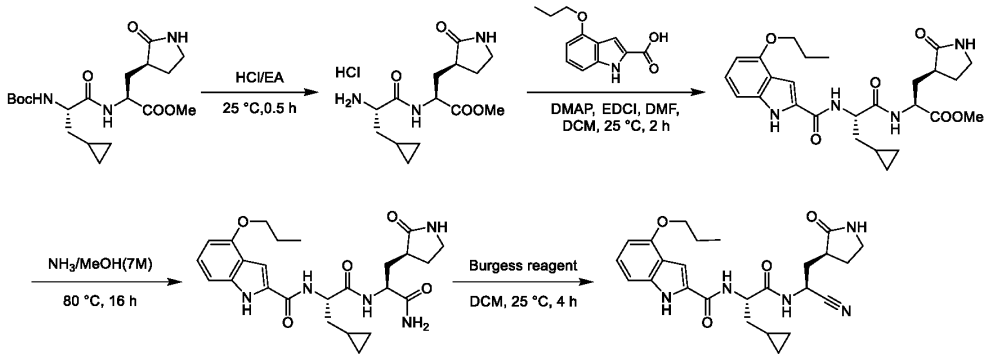
Step 6: N-[(1S)-1-[[1-cyano-2-(1H-indazol-3-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H- indole-2-carboxamide

[000548] To a mixture of N-[(1S)-1-[[1-(1H-indazol-3-ylmethyl)-2-nitroso-ethyl]carbamoyl]-3-methyl-butyl] -4-methoxy-1H-indole-2-carboxamide (75 mg, 152.89 umol, 1 *eq*) in DCM (0.5 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (75.00 mg, 314.72 umol, 2.06 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated and purified by pre-HPLC. N-[(1S)-1-[[1-cyano-2-(1H- indazol-3-yl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (12.0 mg, 25.39 umol, 16.61% yield) was obtained as a white solid. MS (ESI) *m/z* 473.2 $[M+H]^+$

[000549] Prep-HPLC condition:column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10Mm NH_4HCO_3)-ACN]; B%: 28%-58%,10min

[000550] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.95 (br d, *J* = 8.82 Hz, 1 H), 11.59 (br dd, *J* = 6.50, 1.87 Hz, 1 H), 9.02 (br dd, *J* = 14.11, 7.94 Hz, 1 H), 8.39 - 8.51 (m, 1 H), 7.82 (dd, *J* = 11.14, 8.27 Hz, 1 H), 7.48 - 7.55 (m, 1 H), 7.31 - 7.41 (m, 1 H), 7.07 - 7.16 (m, 2 H), 6.99 - 7.05 (m, 1 H), 6.49 - 6.56 (m, 1 H), 5.24 (quin, *J* = 7.77 Hz, 1 H), 4.39 - 4.57 (m, 1 H), 3.90 (d, *J* = 3.97 Hz, 3 H), 3.37 - 3.62 (m, 2 H), 1.60 - 1.73 (m, 1 H), 1.43 - 1.53 (m, 1 H), 1.15 - 1.28 (m, 1 H), 0.84 - 0.98 (m, 3 H), 0.80 (d, *J* = 6.39 Hz, 2 H)

Example 53. Synthesis of viral protease inhibitor compound 1045



Step 1: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000551] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.3 g, 3.27 mmol, 1 *eq*) in HCl/MeOH (10 mL) was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure to give crude methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (900 mg, 3.03 mmol, 92.54% yield) as a yellow oil.

Step 2: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-propoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000552] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (448 mg, 1.51 mmol, 1 *eq*) and 4-propoxy-1H-indole-2-carboxylic acid (396.37 mg, 1.81 mmol, 1.2 *eq*) in DMF (2 mL) was added DCM (8 mL) and EDCI (866.48 mg, 4.52 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added DMAP (552.19 mg, 4.52 mmol, 3 *eq*) and stirred at 25 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (10 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=5/1 to 0/1) to afford methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-propoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (480 mg, 962.75 umol, 63.90% yield) as a white solid. MS (ESI) *m/z* 499.2 $[M+H]^+$

Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide

[000553] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-propoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (480 mg, 962.75 umol, 1 *eq*) in NH_3/MeOH (7M) (3 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give the crude N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide (380 mg, 785.84 umol, 81.62% yield) as a white solid. MS (ESI) *m/z* 484.3 $[M+H]^+$

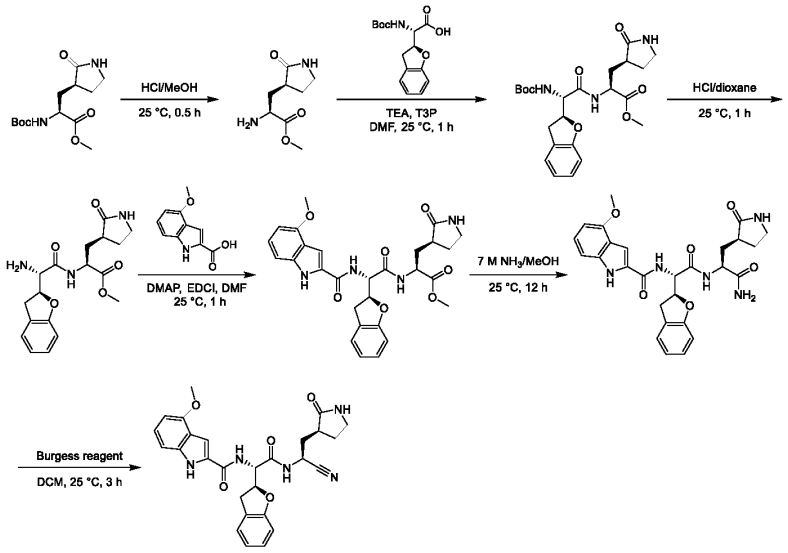
Step 4: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide

[000554] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide (380 mg, 785.84 umol, 1 *eq*) in DCM (7 mL) was added Burgess reagent (1.12 g, 4.72 mmol, 6 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (neutral condition) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide (120 mg, 257.76 umol, 32.80% yield) was obtained as a white solid. MS (ESI) *m/z* 466.3 $[M+H]^+$

[000555] column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min

[000556] ^1H NMR (400MHz, DMSO-d_6) δ = 11.55 (br d, *J*=1.7 Hz, 1H), 9.07 - 8.85 (m, 1H), 8.57 (d, *J*=7.6 Hz, 1H), 7.83 - 7.61 (m, 1H), 7.39 (d, *J*=1.6 Hz, 1H), 7.14 - 6.90 (m, 2H), 6.48 (d, *J*=7.6 Hz, 1H), 5.09 - 4.86 (m, 1H), 4.60 - 4.28 (m, 1H), 4.04 (t, *J*=6.4 Hz, 2H), 3.22 - 3.01 (m, 2H), 2.45 - 2.03 (m, 3H), 1.94 - 1.59 (m, 5H), 1.58 - 1.34 (m, 1H), 1.06 (t, *J*=7.4 Hz, 3H), 0.95 - 0.69 (m, 1H), 0.55 - 0.30 (m, 2H), 0.28 - -0.02 (m, 2H)

Example 54. Synthesis of viral protease inhibitor compound 147



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000557] A solution of (S)-methyl 2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (100 mg, 349.26 umol, 1 eq) in HCl/MeOH (4 M, 2 mL, 22.91*eq*) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated to give the crude product (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate (65 mg, crude) as white solid. MS (ESI) *m/z* 187.1 $[M+H]^+$

Step 2: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-2-((S)-2,3-dihydrobenzofuran-2-yl)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000558] To a mixture of (S)-2-((tert-butoxycarbonyl)amino)-2-((S)-2,3-dihydrobenzofuran-2-yl)acetic acid (100 mg, 340.93 umol, 1 eq) and (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate (65 mg, 349.07 umol, 1.02 eq) in DMF (3 mL) was added TEA (206.99 mg, 2.05 mmol, 284.72 uL, 6 eq) and T_3P (325.43 mg, 511.40 umol, 304.14 uL, 50% purity, 1.5 eq). The reaction was stirred at 25 °C for 1 h, and then diluted with H_2O (20 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-2-((S)-2,3-dihydrobenzofuran-2-yl)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (110 mg, crude) as white solid. MS (ESI) *m/z* 462.2 $[M+H]^+$

Step 3: (S)-methyl 2-((S)-2-amino-2-((S)-2,3-dihydrobenzofuran-2-yl)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000559] A solution of (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-2-((S)-2,3-dihydrobenzofuran-2-yl)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (110 mg, 238.35 umol, 1 eq) in HCl/dioxane (2 mL) was stirred at 25°C for 1 h. The residue was concentrated in vacuum to afford (S)-methyl 2-((S)-2-amino-2-((S)-2,3-dihydrobenzofuran-2-yl)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (95 mg, crude, HCl) as white solid. MS (ESI) *m/z* 362.2 $[M+H]^+$

Step 4: (S)-methyl 2-((S)-2-((S)-2,3-dihydrobenzofuran-2-yl)-2-(4-methoxy-1H-indole-2-carboxamido)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000560] To a solution of (S)-methyl 2-((S)-2-amino-2-((S)-2,3-dihydrobenzofuran-2-yl)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (95 mg, 238.78 umol, 1 eq, HCl)

and 4-methoxy-1H-indole-2-carboxylic acid (45.65 mg, 238.78 umol, 1 eq) in DMF (3 mL) was added EDCI (91.55 mg, 477.56 umol, 2 eq) and DMAP (58.34 mg, 477.56 umol, 2 eq) then was stirred at 25 °C for 1 h. The residue was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (10 mL*3). The combined organic phase was washed with brine (10 mL*3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by *prep*-HPLC column: Waters Xbridge BEH C18 100*25 mm*5 um; mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 20%-50%,10 min to give (S)-methyl 2-((S)-2-((S)-2,3-dihydrobenzofuran-2-yl)-2-(4-methoxy-1H-indole-2-carboxamido)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (21 mg, 39.28 umol, 16.45% yield) as light yellow solid. MS (ESI) *m/z* 535.2 $[M+H]^+$

Step 5: -((S)-2-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-((S)-2,3-dihydrobenzofuran-2-yl)-2-oxoethyl)-4-methoxy-1H-indole-2-carboxamide

[000561] A solution of (S)-methyl 2-((S)-2-((S)-2,3-dihydrobenzofuran-2-yl)-2-(4-methoxy-1H-indole-2-carboxamido)acetamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (19 mg, 35.54 umol, 1 eq) in NH_3.MeOH (7 M, 5 mL, 984.71 eq) was stirred at 25 °C for 12 h. The reaction was concentrated to afford N-((S)-2-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-((S)-2,3-dihydrobenzofuran-2-yl)-2-oxoethyl)-4-methoxy-1H-indole-2-carboxamide (19 mg, crude) as white solid. MS (ESI) *m/z* 520.1 $[M+H]^+$

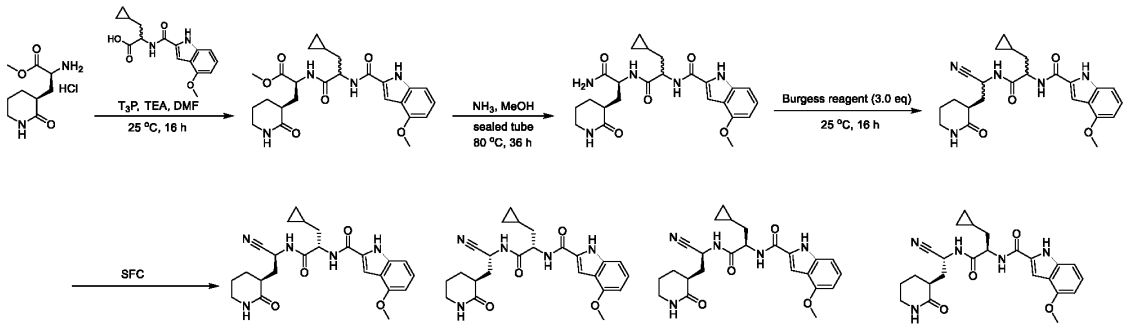
Step 6: N-((S)-2-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-1-((S)-2,3-dihydrobenzofuran-2-yl)-2-oxoethyl)-4-methoxy-1H-indole-2-carboxamide

[000562] A mixture of N-((S)-2-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-((S)-2,3-dihydrobenzofuran-2-yl)-2-oxoethyl)-4-methoxy-1H-indole-2-carboxamide (19 mg, 36.57 umol, 1 eq), methoxycarbonyl-(triethylammonio)sulfonyl-azanide (26.14 mg, 109.71 umol, 3 eq) in DCM (2 mL) was stirred at 25 °C for 3 h. The reaction mixture was concentrated and purified by *prep*-HPLC column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 20%-50%, 8 min to give N-((S)-2-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-1-((S)-2,3-dihydrobenzofuran-2-yl)-2-oxoethyl)-4-methoxy-1H-indole-2-

carboxamide (2.13 mg, 3.74 umol, 10.22% yield, 88% purity) as white solid. MS (ESI) *m/z* 502.2 $[M+H]^+$.

[000563] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.29 - 7.32 (m, 1 H) 7.19 - 7.25 (m, 1 H) 7.17 (d, *J*=8.07 Hz, 1 H) 7.08 - 7.14 (m, 1 H) 7.05 (d, *J*=8.31 Hz, 1 H) 6.87 (t, *J*=7.40 Hz, 1 H) 6.74 (d, *J*=7.95 Hz, 1 H) 6.54 (d, *J*=7.70 Hz, 1 H) 5.04 - 5.24 (m, 2 H) 4.71 - 4.78 (m, 1 H) 4.63 (s, 1 H) 3.96 (s, 3 H) 3.35 - 3.51 (m, 2 H) 3.06 - 3.30 (m, 2 H) 2.68 (ddt, *J*=14.09, 9.63, 4.83, 4.83 Hz, 0.4 H) 2.24 - 2.45 (m, 2 H) 2.13 - 2.22 (m, 0.6 H) 1.70 - 1.94 (m, 2 H)

Example 55. Synthesis of viral protease inhibitor compound 491



Step 1: methyl (2S)-2-[[3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000564] To the mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (240 mg, 1.01 mmol, 1 *eq*, HCl), (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (412.2 mg, 1.22 mmol, 1.2 *eq*, HCl) and TEA (410.4 mg, 4.06 mmol, 0.56 mL, 4 *eq*) in DMF (3 mL) was added T_3P (1.2 g, 2.03 mmol, 1.21 mL, 50% purity, 2 *eq*) at 25 °C. The mixture was stirred at 25 °C for 16 h. TLC (DCM:MeOH =10:1/UV254nm) showed new spot was detected. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 100~25% Ethyl acetate/MeOH@ 30 mL/min). Compound methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-

piperidyl]propanoate (256 mg, 0.48 mmol, 48.2% yield, 92.5% purity) was obtained as yellow solid.

Step 2: N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000565] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (246.3 mg, 0.47 mmol, 92.5% purity, 1 *eq*) in NH_3 (7 M, 6.72 mL, 100 *eq*) (7M in MeOH) was stirred at 80 °C for 36 h in a sealed tube. LC-MS showed the desired compound was detected. The reaction mixture was concentrated in vacuum. Compound N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (220 mg, crude) was obtained as yellow solid, which was used into the next step without further purification.

Step 3: N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000566] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (250 mg, 0.53 mmol, 1 *eq*) and methoxycarbonyl-(triethylammonio)sulfonyl-azanide (444.0 mg, 1.86 mmol, 3.5 *eq*) in DCM (3 mL) was stirred at 25 °C for 16 h. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 23%-53%, 9.5 min). Compound N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (83 mg, 0.18 mmol, 34.2% yield, 99.0% purity) was obtained as white solid.

[000567] Isomer 1: *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide

[000568] Isomer 2: *N*-[(1*S*)-2-[[(1*R*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide

[000569] Isomer 3: *N*-[(1*R*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide

[000570] Isomer 4: *N*-[(1*R*)-2-[[(1*R*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide

[000571] N-[2-[[1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (50 mg, 0.11mmol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 55%-55%,min) to get three fragments.

[000572] Isomer 1: *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide. Compound N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (28.1 mg, 62.2 umol, 56.2% yield, 100% purity) was obtained as white solid. LCMS： Rt = 0.755min; for $C_{24}H_{29}N_5O_4$ MS Calcd.: 451.22, MS Found: 452.2 [$M+H^+$].

[000573] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 8.91 (br d, *J* = 8.0 Hz, 1H), 8.50 (br d, *J* = 7.5 Hz, 1H), 7.53 (br s, 1H), 7.37 (d, *J* = 1.4 Hz, 1H), 7.15 - 7.06 (m, 1H), 7.04 - 6.97 (m, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 5.07 (q, *J* = 8.2 Hz, 1H), 4.49 - 4.40 (m, 1H), 3.89 (s, 3H), 3.15 - 3.01 (m, 2H), 2.34 - 2.20 (m, 2H), 1.91 - 1.76 (m, 3H), 1.70 (br dd, *J* = 4.4, 8.7 Hz, 1H), 1.64 - 1.53 (m, 1H), 1.35 (br s, 1H), 0.86 - 0.76 (m, 1H), 0.48 - 0.35 (m, 2H), 0.25 - 0.04 (m, 2H).

[000574] Isomer 4: *N*-[(1*R*)-2-[[(1*R*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide. Compound N-[(1R)-2-[[(1R)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (6.1 mg, 13.5 umol, 12.2% yield, 100% purity) was obtained as white solid. LCMS： Rt = 0.752min; for $C_{24}H_{29}N_5O_4$ MS Calcd.: 451.22, MS Found: 452.2 [$M+H^+$].

[000575] ^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (s, 1H), 7.18 - 7.12 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 5.12 (dd, *J* = 6.4, 7.7 Hz, 1H), 4.85 (br s, 1H), 3.93 (s, 3H), 3.24 - 3.16 (m, 2H), 2.50 - 2.32 (m, 2H), 2.06 - 1.92 (m, 2H), 1.92 - 1.82 (m, 2H),

1.70 (dt, *J* = 7.0, 14.2 Hz, 2H), 1.63 - 1.54 (m, 1H), 1.31 - 1.31 (m, 1H), 1.41 - 1.27 (m, 1H), 0.91 - 0.80 (m, 1H), 0.53 (br d, *J* = 8.0 Hz, 2H), 0.25 - 0.14 (m, 2H).

[000576] The mixture of Isomer 2 & Isomer 3 (20.0 mg, 44.3 umol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALCEL OD-H(250mm*30mm,5um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 45%-45%,min) to get two fragments.

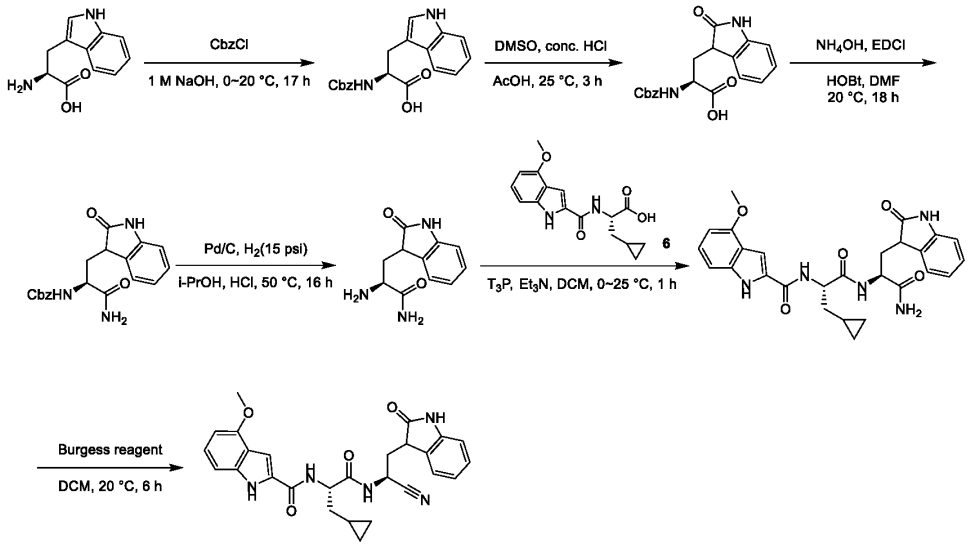
[000577] Isomer 3: N-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide. Compound N-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (5.1 mg, 11.3 umol, 25.6% yield, 100% purity) was obtained as white solid. LCMS： Rt = 0.754min; for $C_{24}H_{29}N_5O_4$ MS Calcd: 451.22, MS Found: 452.1 [$M+H^+$].

[000578] ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1H), 7.18 - 7.12 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.06 (dd, *J* = 6.5, 9.8 Hz, 1H), 4.81 (br s, 1H), 3.93 (s, 3H), 3.18 (br s, 2H), 2.43 - 2.35 (m, 1H), 2.45 - 2.27 (m, 1H), 2.31 (br s, 1H), 2.06 - 1.95 (m, 1H), 1.94 - 1.78 (m, 3H), 1.76 - 1.59 (m, 2H), 1.58 - 1.45 (m, 1H), 1.40 (s, 1H), 1.29 (s, 1H), 0.92 - 0.79 (m, 1H), 0.58 - 0.44 (m, 2H), 0.26 - 0.12 (m, 2H).

[000579] Isomer 2: *N*-[(1*S*)-2-[[(1*R*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide. Compound N-[(1S)-2-[[(1R)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (6.3 mg, 14.0 umol, 31.6% yield, 100% purity) was obtained white solid. LCMS： Rt = 0.754min; for $C_{24}H_{29}N_5O_4$ MS Calcd: 451.22, MS Found: 452.1 [$M+H^+$].

[000580] ^{1}H NMR (400 MHz, CD_3OD) δ 7.12 (s, 1H), 7.01 - 6.96 (m, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 4.89 (t, *J* = 7.2 Hz, 1H), 4.43 (dd, *J* = 6.3, 8.3 Hz, 2H), 3.77 (s, 3H), 3.08 - 3.00 (m, 2H), 2.32 - 2.22 (m, 1H), 2.20 - 2.10 (m, 1H), 2.27 - 2.07 (m, 1H), 1.84 - 1.73 (m, 2H), 1.72 - 1.62 (m, 2H), 1.60 - 1.50 (m, 2H), 1.43 - 1.34 (m, 1H), 0.75 - 0.62 (m, 1H), 0.40 - 0.27 (m, 2H), 0.08 -0.04 (m, 2H).

Example 56. Synthesis of viral protease inhibitor compound 247



Step 1: (2S)-2-(benzyloxycarbonylamino)-3-(1H-indol-3-yl)propanoic acid

[000581] (2S)-2-amino-3-(1H-indol-3-yl)propanoic acid (3 g, 14.69 mmol, 1 eq) was dissolved in NaOH (1 M, 14.65 mL) and stirred at 0 °C. CbzCl (2.51 g, 14.73 mmol, 2.09 mL, 1 eq) and NaOH (1 M, 14.65 mL) were then simultaneously added drop-wise. The mixture was stirred for 17 h at 20 °C. Upon completion, the solution was acidified with 6 M HCl to pH = 1 after which the product was extracted with EtOAc (80 mL * 3). The organic layers were combined, dried by Na_2SO_4 and evaporated. The crude product was purified by silica gel chromatography (SiO_2, DCM:MeOH = 7:1) and re-purified by prep-HPLC (HPLC:ET40319-84-P1D; column: Xtimate C18 10u 250mm*80mm;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 5%-35%,25min) to give (2S)-2-(benzyloxycarbonylamino)-3-(1H-indol-3-yl)propanoic acid (1.6 g, 4.63 mmol, 31.55% yield, 98% purity) as light yellow solid. MS (ESI) m/z 339.1 $[M+H]^+$

[000582] ^1H NMR (400MHz, DMSO-d_6) δ = 10.79 (br s, 1H), 7.57 - 7.44 (m, 1H), 7.35 - 7.23 (m, 5H), 7.21 - 7.13 (m, 1H), 7.10 (d, J=2.1 Hz, 1H), 7.07 - 7.01 (m, 1H), 6.98 - 6.88 (m, 2H), 6.98 - 6.88 (m, 1H), 4.97 (s, 2H), 4.09 (dt, J=4.6, 7.7 Hz, 1H), 3.22 (dd, J=4.3, 14.4 Hz, 1H), 3.00 (dd, J=8.0, 14.5 Hz, 1H).

Step 2: (2S)-2-(benzyloxycarbonylamino)-3-(2-oxoindolin-3-yl)propanoic acid

[000583] A mixture of (2S)-2-(benzyloxycarbonylamino)-3-(1H-indol-3-yl)propanoic acid (1.5 g, 4.00 mmol, 1 eq, HCl) in AcOH (60 mL) was added DMSO (469.01 mg, 6.00 mmol, 469.01 uL, 1.5 eq) and HCl (12 M, 1.33 mL, 4 eq) at 25 °C, and the mixture was

stirred at 25 °C for 3 h under N_2. Upon completion, the mixture was quenched with water (100 mL), extracted with ethyl acetate (60 mL * 3), the combined organic layer washed with brine (200 mL), dried with Na_2SO_4, filtered and concentrated in reduced pressure at 40 °C. The mixture was purified by prep-HPLC (column: Welch Xtimate C18 250*70mm#10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 7%-37%,20min) to give (2S)-2-(benzyloxycarbonylamino)-3-(2-oxoindolin-3-yl)propanoic acid (800 mg, 2.03 mmol, 50.77% yield, 90% purity) as white solid. MS (ESI) m/z 337.0 $[M+H]^+$

Step 3: benzyl N-[(1S)-2-amino-2-oxo-1-[(2-oxoindolin-3-yl)methyl]ethyl]carbamate

[000584] A mixture of (2S)-2-(benzyloxycarbonylamino)-3-(2-oxoindolin-3-yl)propanoic acid (600 mg, 1.54 mmol, 1 eq, HCl) in DMF (20 mL) was added 1-hydroxybenzotriazole (207.45 mg, 1.54 mmol, 1 eq) and EDCI (323.74 mg, 1.69 mmol, 1.1 eq) at 20 °C. After the mixture was stirred at 20 °C for 2 h under N_2, $NH_3.H_2O$ (1.01 g, 7.22 mmol, 1.11 mL, 25% purity, 4.7 eq) was added drop-wise. The mixture was stirred at 20 °C for 16 h. Upon completion, the mixture quenched with water (30 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated in reduced pressure at 40 °C to give benzyl N-[(1S)-2-amino-2-oxo-1-[(2-oxoindolin-3-yl)methyl]ethyl]carbamate (500 mg, crude) as white solid which was used for next step without further purification. MS (ESI) m/z 354.1 $[M+H]^+$

Step 4: (2S)-2-amino-3-(2-oxoindolin-3-yl)propanamide

[000585] To a solution of benzyl N-[(1S)-2-amino-2-oxo-1-[(2-oxoindolin-3-yl)methyl]ethyl]carbamate (500 mg, 1.41 mmol, 1 eq) in i-PrOH (100 mL) was added Pd/C (339.59 mg, 282.99 umol, 10% purity, 0.2 eq) and HCl (12 M, 1.30 mL, 11 eq) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 50 °C for 16 h. Upon completion, the reaction mixture was filtered and the filter was concentrated. The crude product was purified by prep-HPLC (HPLC: ET40319-96-P1C; column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 1%-20%,8min) to give (2S)-2-amino-3-(2-oxoindolin-3-yl)propanamide (130 mg, 549.67 umol, 38.85% yield, 92.7% purity) as white solid. MS (ESI) m/z 220.1 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(2-oxoindolin-3-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000586] To a mixture of (2S)-2-amino-3-(2-oxoindolin-3-yl)propanamide (60 mg, 273.67 umol, 1 eq), (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (99.29 mg, 328.41 umol, 1.2 eq) and Et_3N (166.16 mg, 1.64 mmol, 228.55 uL, 6 eq) in DCM (10 mL) was added T3P (522.46 mg, 821.02 umol, 488.28 uL, 50% purity, 3 eq) drop-wise at 0 °C. The solution was stirred at 25 °C for 1 h under N_2. Upon completion, the mixture was quenched with water (20 mL) and extracted with DCM:MeOH = 7:1 (15 mL * 2). The combined organic layers washed with brine (30 mL), dried with Na_2SO_4, filtered and concentrated in reduced pressure at 40 °C. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(2-oxoindolin-3-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (40 mg, 55.61 umol, 20.32% yield, 70% purity) as colorless oil. MS (ESI) m/z 504.3 $[M+H]^+$

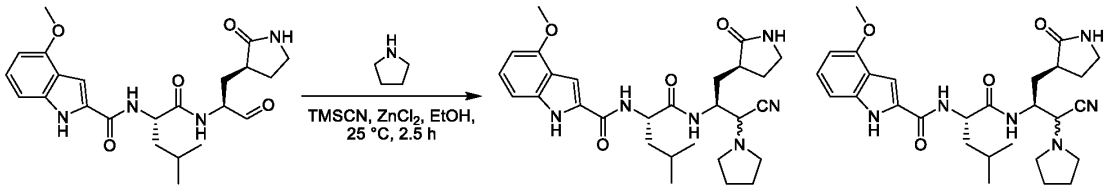
Step 6: N-[(1S)-2-[[(1S)-1-cyano-2-(2-oxoindolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000587] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(2-oxoindolin-3-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (35 mg, 69.51 umol, 1 eq) in DCM (6 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (49.69 mg, 208.52 umol, 3 eq) in one portion at 20 °C and stirred at 20 °C for 2 h. Methoxycarbonyl-(triethylammonio)sulfonyl-azanide (82.82 mg, 347.53 umol, 5 eq) was added at 20 °C and stirred at 20 °C for 4 h. Upon completion, the crude was dried by N_2 and purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min) and re-purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 30%-70%,8min) to afford N-[(1S)-2-[[(1S)-1-cyano-2-(2-oxoindolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (5 mg, 10.23 umol, 14.72% yield, 99.36% purity, 99.36% purity) as white solid. MS (ESI) m/z 486.2 $[M+H]^+$

[000588] ^1H NMR (400MHz, METHANOL-d_4) δ = 7.39 - 7.09 (m, 4H), 7.07 - 6.95 (m, 2H), 6.92 - 6.80 (m, 1H), 6.51 (dd, J=3.1, 7.5 Hz, 1H), 5.37 - 5.14 (m, 1H), 4.65 - 4.47

(m, 1H), 3.93 (dd, J=1.4, 3.4 Hz, 3H), 3.70 - 3.52 (m, 1H), 2.63 - 2.27 (m, 2H), 1.92 - 1.60 (m, 2H), 0.84 (br s, 1H), 0.59 - 0.43 (m, 2H), 0.27 - 0.10 (m, 2H)

Example 57. Synthesis of viral protease inhibitor compound 331



Steps for Isomer 1 and 2: N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2-pyrrolidin-1-yl-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

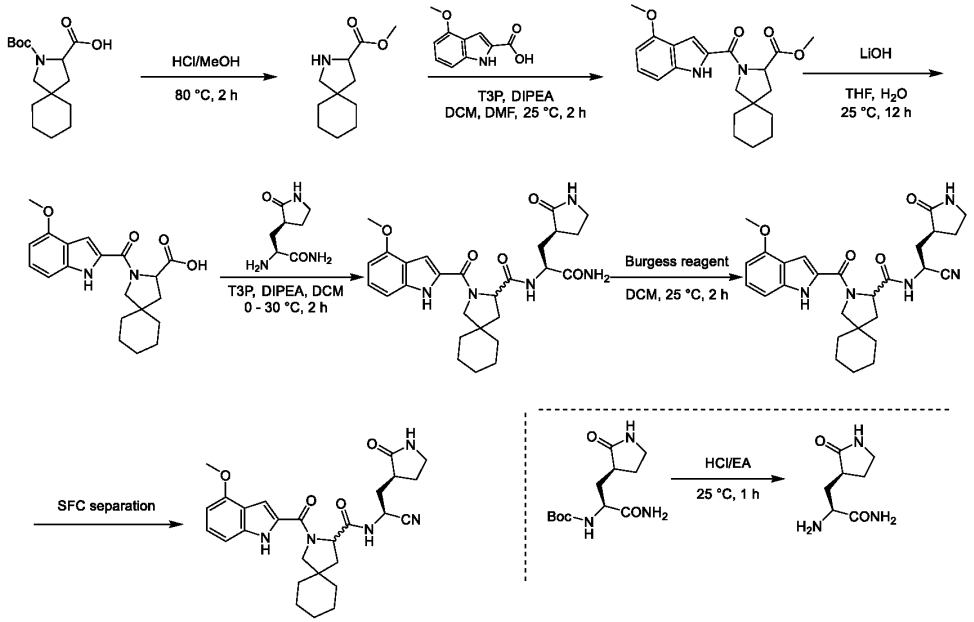
[000589] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl] -3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (700 mg, 1.27 mmol, 80% purity, 1 eq) in EtOH (10 mL) was added pyrrolidine (180.01 mg, 2.53 mmol, 211.28 uL, 2 eq) and ZnCl2 (1 M, 12.66 uL, 0.01 eq). The mixture was stirred at 25 °C for 30 min, and then added TMSCN (251.10 mg, 2.53 mmol, 316.65 uL, 2 eq). The mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC to get the compound N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2-pyrrolidin-1-yl-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (110 mg, 199.95 umol, 15.80% yield, 95% purity) and N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2-pyrrolidin-1-yl-ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (110 mg, 199.95 umol, 15.80% yield, 95% purity) as white solid. MS (ESI) m/z 523.4 $[M+H]^+$

[000590] column: Phenomenex luna CN 5u 100*30mm;mobile phase: [Hexane-IPA];B%: 5%-40%,20min

[000591] Isomer 1: ^{1}H NMR (400MHz, DMSO-d6) δ = 11.58 (s, 1H), 8.43 (d, J=7.7 Hz, 1H), 8.20 (d, J=9.4 Hz, 1H), 7.68 - 7.49 (m, 1H), 7.38 (d, J=1.2 Hz, 1H), 7.18 - 6.93 (m, 2H), 6.50 (d, J=7.6 Hz, 1H), 4.57 - 3.99 (m, 3H), 3.88 (s, 3H), 3.19 - 2.95 (m, 2H), 2.64 - 2.53 (m, 4H), 2.38 - 2.27 (m, 1H), 2.15 - 2.01 (m, 1H), 1.85 - 1.44 (m, 10H), 0.91 (dd, J=6.4, 16.3 Hz, 6H)

[000592] Isomer 2: ^{1}H NMR (400MHz, DMSO-d6) δ = 11.59 (br s, 1H), 8.39 (br d, J=7.6 Hz, 1H), 8.01 (br d, J=9.1 Hz, 1H), 7.69 - 7.49 (m, 1H), 7.43 - 7.28 (m, 1H), 7.16 - 6.86 (m, 2H), 6.50 (d, J=7.6 Hz, 1H), 4.59 - 4.24 (m, 3H), 3.88 (s, 3H), 3.19 - 2.94 (m, 2H), 2.71 - 2.57 (m, 2H), 2.49 - 2.32 (m, 3H), 2.18 - 2.08 (m, 1H), 2.06 - 1.93 (m, 1H), 1.83 - 1.37 (m, 9H), 0.90 (dd, J=6.5, 15.2 Hz, 6H)

Example 58. Synthesis of viral protease inhibitor compound 389



Step 1: (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide

[000593] *tert*-butyl *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamate (2 g, 7.37 mmol, 1 eq) in HCl/EtOAc (4 M, 50 mL, 27.13 eq) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure to afford (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (1.2 g, crude) as a white solid.

Step 2: methyl 2-azaspiro[4.5]decane-3-carboxylate

[000594] 2-*tert*-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (3 g, 10.59 mmol, 1 eq) was added in HCl/MeOH (4 M, 50 mL, 18.89 eq). The mixture was stirred at

80 °C for 2 h. The mixture was concentrated under the reduced pressure affording the product methyl 2-azaspiro[4.5]decane-3-carboxylate (2 g, crude) as a yellow oil.

Step 3: methyl 2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate

[000595] To a solution of methyl 2-azaspiro[4.5]decane-3-carboxylate (2 g, 10.14 mmol, 1 eq) and 4-methoxy-1*H*-indole-2-carboxylic acid (2.33 g, 12.17 mmol, 1.2 eq) in DCM (30 mL) and DMF (5 mL) was added T3P (12.90 g, 20.28 mmol, 12.06 mL, 50% purity, 2 eq) and DIEA (3.93 g, 30.41 mmol, 5.30 mL, 3 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (100 mL) and extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 10:1 to 0:1) affording the product methyl 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate (3 g, 8.10 mmol, 79.88% yield) as a white solid. MS (ESI) *m/z* 371.1 $[M+H]^+$

Step 4: 2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid

[000596] To a solution of methyl 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate (3 g, 8.10 mmol, 1 eq) in THF (45 mL) and H_2O (15 mL) was added $LiOH.H_2O$ (1.70 g, 40.49 mmol, 5 eq). The mixture was stirred at 25 °C for 12 h. Upon completion, the mixture was quenched by addition H_2O (50 mL), and then added aq. HCl (1 M) to adjust the pH = 3 - 4, and extracted with ethyl acetate (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure affording the product 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (2.6 g, crude) as a white solid. MS (ESI) *m/z* 357.1 $[M+H]^+$

Step 5: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000597] To a solution of 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (1 g, 2.81 mmol, 1 eq) and (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (720.49 mg, 4.21 mmol, 1.5 eq) in DCM (30 mL) was added T3P (3.57 g, 5.61 mmol, 3.34 mL, 50% purity, 2 eq) and DIEA (1.09 g, 8.42 mmol, 1.47 mL, 3 eq) at 0 °C. The mixture was stirred at 30 °C for 1 h. Upon completion, the mixture was

quenched by the addition of H_2O (100 mL), and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1:0 to 10:1) affording the product *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (700 mg, 1.37 mmol, 48.96% yield) as a white solid. MS (ESI) *m/z* 510.3 $[M+H]^+$

Step 6: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000598] To a solution of *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (700 mg, 1.37 mmol, 1 eq) in DCM (10 mL) was added Burgess reagent (982.03 mg, 4.12 mmol, 3 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250 * 50 mm * 10 um); mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 10 min) affording the product *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (500 mg, 1.02 mmol, 74.05% yield) as a white solid. MS (ESI) *m/z* 492.3 $[M+H]^+$

Step 7: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000599] *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (500 mg, 1.02 mmol) was separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O IPA]; B%: 55% - 55%, 9 min) affording the product *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (264 mg, 537.04 umol, 52.80% yield, 100% purity) as a white solid. MS (ESI) *m/z* 492.3 $[M+H]^+$

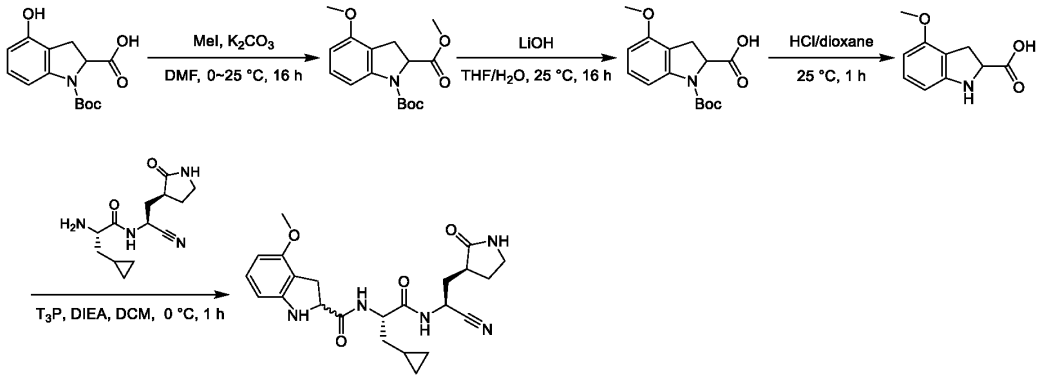
[000600] ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.28 - 6.76 (m, 3H), 6.60 - 6.38 (m, 1H), 5.05 (br dd, *J* = 5.2, 10.2 Hz, 1H), 4.63 – 4.60 (m, 1H), 4.03 - 3.85 (m, 5H), 3.74 -

3.28 (m, 1H), 2.73 (br dd, *J* = 5.0, 8.6 Hz, 1H), 2.51 - 2.28 (m, 2H), 2.27 - 2.08 (m, 1H), 1.96 - 1.72 (m, 2H), 1.69 - 1.38 (m, 11H), 1.37 - 1.09 (m, 1H).

[000601] *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 2 (140 mg, 284.51 umol, 27.97% yield, 99.9% purity) as a white solid. MS (ESI) *m/z* 492.3 $[M+H]^+$

[000602] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.30 - 6.81 (m, 3H), 6.53 (br d, *J* = 2.0 Hz, 1H), 5.12 - 4.95 (m, 2H), 4.70 - 4.55 (m, 2H), 4.08 - 3.86 (m, 4H), 3.84 - 3.72 (m, 1H), 2.62 - 2.40 (m, 1H), 2.36 - 2.18 (m, 2H), 1.94 - 1.69 (m, 3H), 1.68 - 1.34 (m, 11H).

Example 59. Synthesis of viral protease inhibitor compound 513



Step 1: O1-tert-butyl O2-methyl 4-methoxyindoline-1,2-dicarboxylate

[000603] A mixture of 1-tert-butoxycarbonyl-4-hydroxy-indoline-2-carboxylic acid (300 mg, 1.07 mmol, 1 *eq*) in DMF (4 mL) was added K_2CO_3 (445.37 mg, 3.22 mmol, 3 *eq*), and the mixture was added with MeI (381.16 mg, 2.69 mmol, 167.18 uL, 2.5 *eq*) at 0 °C. After stirring at 25 °C for 16 h, the reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (10 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5/1) to give O1-tert-butyl O2-methyl 4-methoxyindoline-1,2-dicarboxylate (220 mg, 715.82 umol, 66.64% yield) as a yellow solid. MS (ESI) *m/z* 208.0 $[M+H-Boc]^+$

Step 2: 1-tert-butoxycarbonyl-4-methoxy-indoline-2-carboxylic acid

[000604] A mixture of O1-tert-butyl O2-methyl 4-methoxyindoline-1,2-dicarboxylate (200 mg, 650.74 umol, 1 *eq*) in THF (1 mL) and H_2O (1 mL) was added LiOH (46.75 mg, 1.95 mmol, 3 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was adjusted to acidity by HCI solution and extracted with ethyl acetate (2 mL * 3). The combined organic layers were washed with brine (5 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1-tert-butoxycarbonyl-4-methoxy-indoline-2-carboxylic acid (175 mg, 596.63 umol, 45.84% yield) as a yellow oil. MS (ESI) *m/z* 237.9 $[M+H-56]^+$

Step 3: 4-methoxyindoline-2-carboxylic acid

[000605] To a mixture of 1-tert-butoxycarbonyl-4-methoxy-indoline-2-carboxylic acid (150 mg, 511.40 umol, 1 eq) was added HCl/dioxane (4 M, 7.50 mL, 58.66 eq). The reaction was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue and used next step directly to get the compound 4-methoxyindoline-2-carboxylic acid (110 mg, 431.07 umol, 84.29% yield, 90% purity, HCl) as yellow oil. MS (ESI) *m/z* 194.1 $[M+H]^+$

Step 4: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2 -oxo-ethyl]-4-methoxy-indoline-2-carboxamide

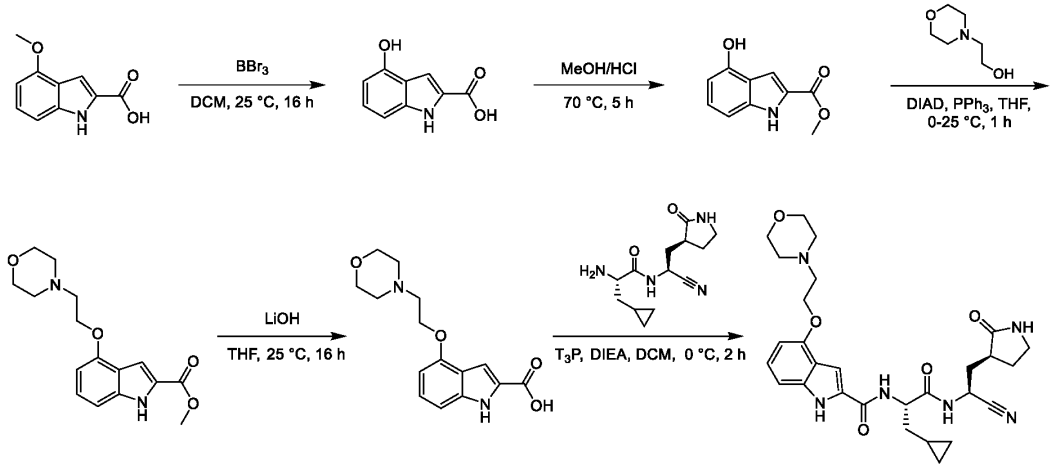
[000606] To a mixture of 4-methoxyindoline-2-carboxylic acid (110 mg, 478.97 umol, 1 eq, HCl) and (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (316.51 mg, 478.97 umol, 40% purity, 1 eq) in DCM (8 mL) was added DIEA (123.81 mg, 957.94 umol, 166.86 uL, 2 eq) and T_3P (457.20 mg, 718.45 umol, 427.29 uL, 50% purity, 1.5 eq) at 0°C. The mixture was stirred at 0 °C for 1 h. The mixture was stirred with EDTA (10 mL) at 25 °C, The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 2). The combined organic layer was concentrated under reduced pressure to give a residue. The residue was purified with neutral prep-HPLC to get the compound N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-indoline-2-carboxamide (29 mg, 63.81 umol, 13.32% yield, 96.7% purity) and N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-indoline-2-carboxamide (26 mg, 55.61 umol, 11.61% yield, 94% purity) as a white solid. MS (ESI) *m/z* 440.2 $[M+H]^+$

[000607] column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 20%-50%,10min

[000608] ^{1}H NMR (400MHz, DMSO-*d6*) δ = 8.99 - 8.83 (m, 1H), 8.08 - 7.89 (m, 1H), 7.71 (s, 1H), 6.92 (t, *J*=8.0 Hz, 1H), 6.25 (dd, *J*=4.4, 7.9 Hz, 2H), 5.91 (d, *J*=3.5 Hz, 1H), 5.05 - 4.85 (m, 1H), 4.42 - 4.14 (m, 2H), 3.70 (s, 3H), 3.28 - 2.97 (m, 3H), 2.90 - 2.76 (m, 1H), 2.43 - 2.26 (m, 1H), 2.19 - 1.98 (m, 2H), 1.87 - 1.54 (m, 3H), 1.50 - 1.31 (m, 1H), 0.79 - 0.54 (m, 1H), 0.47 - 0.26 (m, 2H), 0.20 -0.10 (m, 2H)

[000609] ^{1}H NMR (400MHz, DMSO-*d6*) δ = 8.88 (d, *J*=7.9 Hz, 1H), 7.95 (d, *J*=8.0 Hz, 1H), 7.70 (s, 1H), 6.93 (t, *J*=8.0 Hz, 1H), 6.26 (dd, *J*=4.5, 7.9 Hz, 2H), 5.92 (d, *J*=3.6 Hz, 1H), 5.08 - 4.84 (m, 1H), 4.50 - 4.17 (m, 2H), 3.70 (s, 3H), 3.27 - 2.99 (m, 3H), 2.88 - 2.72 (m, 1H), 2.40 - 2.25 (m, 1H), 2.17 - 2.02 (m, 2H), 1.87 - 1.57 (m, 3H), 1.51 - 1.39 (m, 1H), 0.70 (br s, 1H), 0.49 - 0.26 (m, 2H), 0.21 -0.14 (m, 2H)

Example 60. Synthesis of viral protease inhibitor compound 515



Step 1: 4-hydroxy-1H-indole-2-carboxylic acid

[000610] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (500 mg, 2.62 mmol, 1 *eq*) in DCM (10 mL) was added BBr_3 (1.31 g, 5.23 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. The mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 2). The combined organic layers were washed with brine 20 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-hydroxy-1H-indole-2-carboxylic acid (200 mg, crude) as a red solid. MS (ESI) *m/z* 176.1 $[M-H]^+$

Step 2: methyl 4-hydroxy-1H-indole-2-carboxylate

[000611] 4-hydroxy-1H-indole-2-carboxylic acid (200 mg, 1.13 mmol, 1 *eq*) was added with HCl/MeOH (4 M, 10 mL, 35.43 *eq*), and the mixture was stirred at 70 °C for 5 h. The reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=9/1 to 8/1) to give methyl 4-hydroxy-1H-indole-2-carboxylate (170 mg, 800.28 umol, 70.89% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 190.1 $[M-H]^+$

Step 3: methyl 4-(2-morpholinoethoxy)-1H-indole-2-carboxylate

[000612] To a mixture of methyl 4-hydroxy-1H-indole-2-carboxylate (300 mg, 1.57 mmol, 1 *eq*) and 2-morpholinoethanol (205.83 mg, 1.57 mmol, 192.37 uL, 1 *eq*) in THF (4 mL) was added PPh_3 (452.73 mg, 1.73 mmol, 1.1 *eq*), DIAD (317.30 mg, 1.57 mmol, 305.10 uL, 1 *eq*) was added at 0 °C under N_2. The mixture was stirred at 25 °C for 60 min. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 2). The combined organic layers were washed with brine (20 mL), filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC(PE:EA=0:1) to give methyl 4-(2-morpholinoethoxy)-1H-indole-2-carboxylate (200 mg, 591.44 umol, 37.69% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 304.9 $[M+H]^+$

Step 4: 4-(2-morpholinoethoxy)-1H-indole-2-carboxylic acid

[000613] To a mixture of methyl 4-(2-morpholinoethoxy)-1H-indole-2-carboxylate (200 mg, 657.16 umol, 1 *eq*) in THF (2 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (41.37 mg, 985.74 umol, 1.5 *eq*) at 25 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude was purified by HCl prep-HPLC to give 4-(2-morpholinoethoxy)-1H-indole-2-carboxylic acid (80 mg, 261.79 umol, 39.84% yield, 95% purity) as a white solid. MS (ESI) *m/z* 289.2 $[M-H]^+$

[000614] column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.04%HCl)-ACN];B%: 1%-32%,6.5min

Step 5: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-(2-morpholinoethoxy)-1H-indole-2-carboxamide

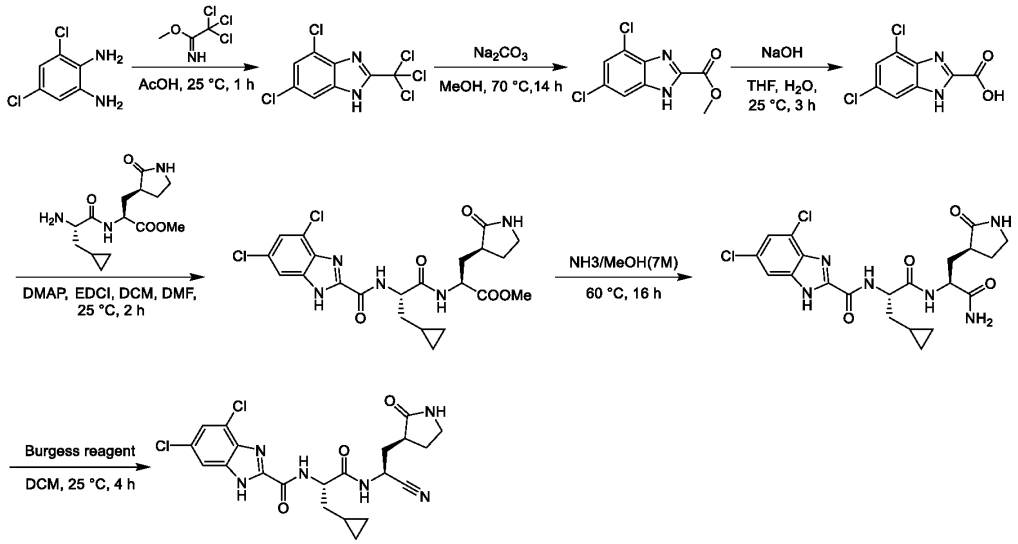
[000615] To a mixture of 4-(2-morpholinoethoxy)-1H-indole-2-carboxylic acid (70 mg, 241.12 umol, 1 *eq*) and (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (159.33 mg, 241.12 umol, 40% purity, 1 *eq*) in DCM (2 mL) was added DIEA (93.49 mg, 723.36 umol, 125.99 uL, 3 *eq*) and T_3P (230.16 mg, 361.68 umol, 215.10 uL, 50% purity, 1.5 *eq*) in one portion at 0 °C, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was added with EDTA solution (2 mL) and stirred at 25 °C for 10 min, and then extracted with DCM (2 mL * 3). The combined organic layers were washed with brine (5 mL * 1), and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-(2-morpholinoethoxy)-1H-indole-2-carboxamide (13 mg, 24.23 umol, 10.05% yield) as a white solid. MS (ESI) *m/z* 537.3 $[M+H]^+$

[000616] column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 20%-50%,8min

[000617] ^1H NMR (400MHz, DMSO-d_6) δ = 11.57 (s, 1H), 8.92 (d, *J*=7.9 Hz, 1H), 8.60 (br d, *J*=7.5 Hz, 1H), 7.79 - 7.68 (m, 1H), 7.35 (d, *J*=1.5 Hz, 1H), 7.14 - 6.93 (m, 2H), 6.51 (d, *J*=7.5 Hz, 1H), 4.98 (q, *J*=7.9 Hz, 1H), 4.54 - 4.38 (m, 1H), 4.21 (br d, *J*=3.5 Hz, 2H), 3.59 (t, *J*=4.5 Hz, 4H), 3.20 - 3.05 (m, 2H), 2.78 (t, *J*=5.6 Hz, 2H), 2.60 - 2.52 (m, 4H), 2.43 - 2.28 (m, 1H), 2.23 - 2.04 (m, 2H), 1.92 - 1.60 (m, 3H), 1.56 - 1.38 (m, 1H), 0.80 (br d, *J*=5.3 Hz, 1H), 0.51 - 0.30 (m, 2H), 0.25 - 0.05 (m, 2H)

[000618] ^1H NMR (400MHz, METHANOL-d_4) δ = 7.34 - 7.28 (m, 1H), 7.18 - 7.11 (m, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 6.53 (d, *J*=7.5 Hz, 1H), 5.08 (dd, *J*=5.8, 10.3 Hz, 1H), 4.54 (t, *J*=7.4 Hz, 1H), 4.30 (t, *J*=5.3 Hz, 2H), 3.77 - 3.72 (m, 4H), 3.30 - 3.27 (m, 2H), 2.92 (t, *J*=5.3 Hz, 2H), 2.75 - 2.59 (m, 5H), 2.40 - 2.26 (m, 2H), 1.99 - 1.79 (m, 3H), 1.78 - 1.60 (m, 1H), 0.93 - 0.76 (m, 1H), 0.58 - 0.52 (m, 2H), 0.20 (br dd, *J*=5.0, 11.6 Hz, 2H)

Example 61. Synthesis of viral protease inhibitor compound 525



Step 1: 4,6-dichloro-2-(trichloromethyl)-1H-benzimidazole

[000619] A mixture of 3,5-dichlorobenzene-1,2-diamine (640.64 mg, 3.62 mmol, 1 *eq*) and methyl 2,2,2-trichloroethanimidate (766.16 mg, 4.34 mmol, 535.78 uL, 1.2 *eq*) in AcOH (5 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (10 mL) and filtered to afford 4,6-dichloro-2-(trichloromethyl)-1H-benzimidazole (860 mg, 2.83 mmol, 78.07% yield) as a brown solid. MS (ESI) *m/z* 304.5 $[M+2H]^+$

Step 2: methyl 4,6-dichloro-1H-benzimidazole-2-carboxylate

[000620] A mixture of 4,6-dichloro-2-(trichloromethyl)-1H-benzimidazole (420 mg, 1.38 mmol, 1 *eq*) in MeOH (5 mL) was added Na_2CO_3 (146.25 mg, 1.38 mmol, 1 *eq*) in one portion at 25 °C. The mixture was heated to 70 °C and stirred for 14 hours. Upon completion, the reaction mixture was diluted with HCl (10 mL) and stirred at 25 °C for 1 h and extracted with ethyl acetate (8 mL * 3). The combined organic layers were washed with brine (10 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give methyl 4,6-dichloro-1H-benzimidazole-2-carboxylate (330 mg, 1.35 mmol, 97.59% yield) as a brown solid. MS (ESI) *m/z* 245.0 $[M+H]^+$

Step 3: 4,6-dichloro-1H-benzimidazole-2-carboxylic acid

[000621] To a mixture of methyl 4,6-dichloro-1H-benzimidazole-2-carboxylate (330 mg, 1.35 mmol, 1 *eq*) in THF (2 mL) and H_2O (2 mL) was added NaOH (161.58 mg, 4.04 mmol, 3 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 3 h. Upon

completion, the reaction mixture was adjusted to acidity with 1M HCl solution (5 mL), and then extracted with ethyl acetate (5 mL * 3). The combined organic layers were washed with brine (10 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4,6-dichloro-1H-benzimidazole-2-carboxylic acid (200 mg, 865.67 umol, 64.29% yield) as a brown solid. MS (ESI) *m/z* 229.0 $[M-H]^+$

Step 4: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,6-dichloro-1H-benzimidazole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000622] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (140 mg, 470.83 umol, 1 *eq*) and 4,6-dichloro-1H-benzimidazole-2-carboxylic acid (197.78 mg, 470.83 umol, 55% purity, 1 *eq*) in DCM (3 mL) and DMF (1 mL) was added DMAP (172.56 mg, 1.41 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added EDCI (270.78 mg, 1.41 mmol, 3 *eq*) and stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O (4 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic layers were washed with brine (8 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (basic condition, column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 30%-60%, 8 min) to give methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,6-dichloro-1H-benzimidazole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (70 mg, 137.16 umol, 29.13% yield) as a white solid. MS (ESI) *m/z* 510.2 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,6-dichloro-1H-benzimidazole-2-carboxamide

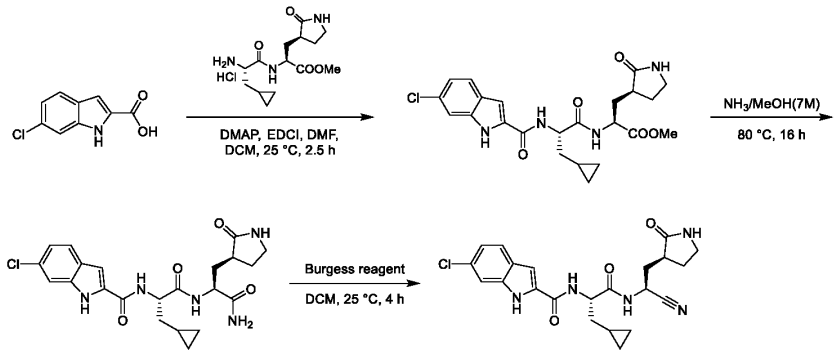
[000623] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,6-dichloro-1H-benzimidazole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (60 mg, 117.56 umol, 1 *eq*) in NH_3/MeOH (7 M, 8 mL, 476.34 *eq*) was stirred at 60 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,6-dichloro-1H-benzimidazole-2-carboxamide (58 mg, 117.09 umol, 99.60% yield) as a white solid. MS (ESI) *m/z* 495.2 $[M+H]^+$

Step 6: 4,6-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-benzimidazole-2-carboxamide

[000624] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,6-dichloro-1H-benzimidazole-2-carboxamide (50 mg, 100.94 umol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (48.11 mg, 201.87 umol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (basic condition, column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 15%-45%,8min) to give 4,6-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-benzimidazole-2-carboxamide (13 mg, 27.23 umol, 26.98% yield) as a white solid. MS (ESI) *m/z* 477.1 $[M+H]^+$

[000625] ^1H NMR (400MHz, DMSO-d_6) δ = 13.77 (br s, 1H), 8.97 - 8.81 (m, 2H), 7.71 (s, 1H), 7.66 - 7.40 (m, 2H), 5.05 - 4.91 (m, 1H), 4.60 - 4.48 (m, 1H), 3.21 - 3.03 (m, 2H), 2.43 - 2.28 (m, 1H), 2.22 - 2.06 (m, 2H), 2.02 - 1.85 (m, 1H), 1.84 - 1.54 (m, 3H), 0.81 - 0.69 (m, 1H), 0.48 - 0.34 (m, 2H), 0.20 - 0.04 (m, 2H)

Example 62. Synthesis of viral protease inhibitor compound 529



Step 1: methyl (2S)-2-[[(2S)-2-[(6-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000626] A mixture of 6-chloro-1H-indole-2-carboxylic acid (800 mg, 4.08 mmol, 1 *eq*) in DCM (6 mL) and DMF (3 mL) was added DMAP (1.50 g, 12.24 mmol, 3 *eq*) in one portion at 25 °C. The mixture added methyl(2S)-2-[[(2S)-2-amino-3-cyclopropyl-

propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.36 g, 4.08 mmol, 1 *eq*, HCl) and EDCI (2.34 g, 12.24 mmol, 3 *eq*) in one portion at 25 °C and stirred for 2.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1). Compound methyl (2S)-2-[[(2S)-2-[(6-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino] -3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (900 mg, 1.89 mmol, 46.45% yield, 90% purity) was obtained as a white solid. MS (ESI) *m/z* 475.1 $[M+H]^+$.

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclo propylmethyl)-2-oxo-ethyl]-6-chloro-1H-indole-2-carboxamide

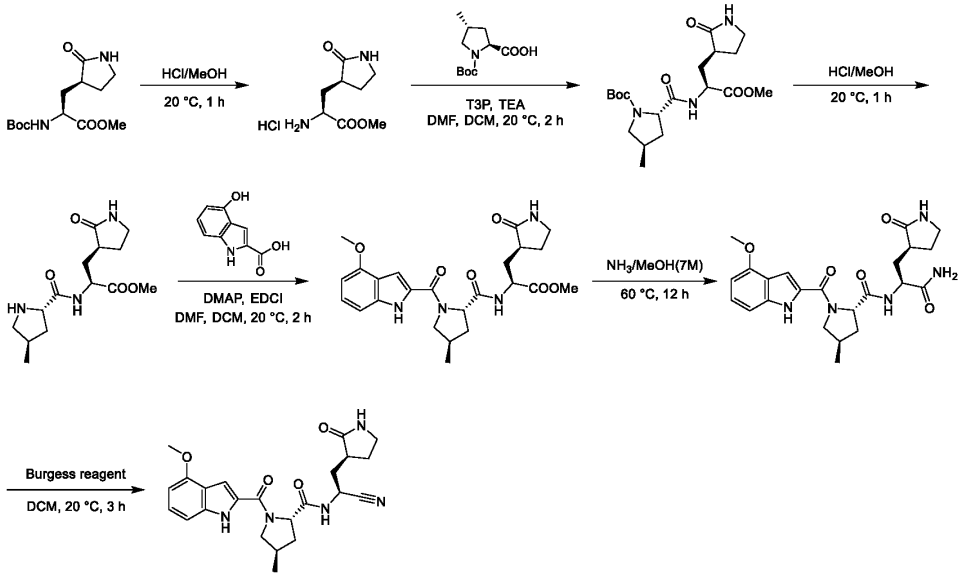
[000627] To a mixture of methyl(2S)-2-[[(2S)-2-[(6-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (900 mg, 1.89 mmol, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 94.99 eq) in one portion at 25 °C. The mixture was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. Compound N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-1H-indole-2-carboxamide (750 mg, crude) was obtained as a white solid and was used fort the next step directly. MS (ESI) *m/z* 460.1 $[M+H]^+$.

Step 3: 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000628] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-1H-indole-2-carboxamide (700 mg, 1.52 mmol, 1 *eq*) in DCM (7 mL) was added Burgess reagent (725.41 mg, 3.04 mmol, 2.5 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min). Compound 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (60 mg, 133.90 umol, 30.79% yield, 98.622% purity) was obtained as a white solid. MS (ESI) *m/z* 442.1 $[M+H]^+$.

[000629] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.74 (br s, 1H), 8.95 (br d, J = 7.72 Hz, 1H), 8.66 (br d, J = 7.28 Hz, 1H), 7.65 - 7.74 (m, 2H), 7.43 (s, 1H), 7.32 (s, 1H), 7.05 (dd, J = 8.49, 1.87 Hz, 1H), 4.95 - 5.03 (m, 1H), 4.47 (br dd, J = 13.67, 7.94 Hz, 1H), 3.07 - 3.18 (m, 2H), 2.31 - 2.41 (m, 1H), 2.07 - 2.18 (m, 2H), 1.65 - 1.89 (m, 3H), 1.42 - 1.54 (m, 1H), 0.80 (br s, 1H), 0.36 - 0.49 (m, 2H), 0.07 - 0.24 (m, 2H), -0.69 - -0.69 (m, 1H)

Example 63. Synthesis of viral protease inhibitor compound 539



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[000630] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.75 mmol, 1 eq) in HCl/MeOH (4 M, 20 mL, 45.81 eq) was stirred at 20 °C for 1 h, and the reaction mixture was concentrated under reduced pressure to afford methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (350 mg, crude, HCl) as a yellow solid.

Step 2: (2S,4R)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4-methylpyrrolidine-1-carboxylate

[000631] To a solution of (2S,4R)-1-tert-butoxycarbonyl-4-methyl-pyrrolidine-2-carboxylic acid (250 mg, 1.09 mmol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (304.45 mg, 1.64 mmol, 1.5 eq) in DCM (10 mL) was added drop-wise T3P (1.04 g, 1.64 mmol, 972.75 uL, 50% purity, 1.5 eq) and Et_3N

(662.02 mg, 6.54 mmol, 910.62 uL, 6 eq), and the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition H_2O (40 mL) at 0 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 10:1 to 0:1) to afford tert-butyl (2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-methyl-pyrrolidine-1-carboxylate (320 mg, 805.10 umol, 73.86% yield) as a colorless oil. MS (ESI) *m/z* 398.2 $[M+H]^+$.

Step 3: (S)-methyl 2-((2S,4R)-4-methylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000632] A solution of tert-butyl (2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-methyl-pyrrolidine-1-carboxylate (260 mg, 654.15 umol, 1 eq) in HCl/MeOH (4 M, 8 mL, 48.92 eq) was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford methyl (2S)-2-[[(2S,4R)-4-methylpyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, crude, HCl) as a colorless oil. MS (ESI) *m/z* 298.2 $[M+H]^+$.

Step 4: (S)-methyl 2-((2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4-methylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000633] To a solution of methyl (2S)-2-[[(2S,4R)-4-methylpyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 599.14 umol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (229.09 mg, 1.20 mmol, 2.0 eq) in DMF (2.0 mL) was added DMAP (219.59 mg, 1.80 mmol, 3.0 eq) and EDCI (229.71 mg, 1.20 mmol, 2 eq) and DCM (8.0 mL), the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition H_2O (50 mL) at 0 °C, and then extracted with DCM (40 mL * 3). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:1 to 0:1) to afford methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 494.14 umol, 82.47% yield, 93% purity) as a yellow solid. MS (ESI) *m/z* 471.3 $[M+H]^+$.

Step 5: (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide

[000634] A solution of methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (220 mg, 434.84 umol, 93% purity, 1 eq) in NH_3/MeOH (7 M, 20 mL, 321.96 eq) was stirred at 60 °C for 12 h. The reaction mixture was concentrated under reduced pressure to afford (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide (200 mg, crude) as a yellow solid. MS (ESI) *m/z* 456.2 $[M+H]^+$.

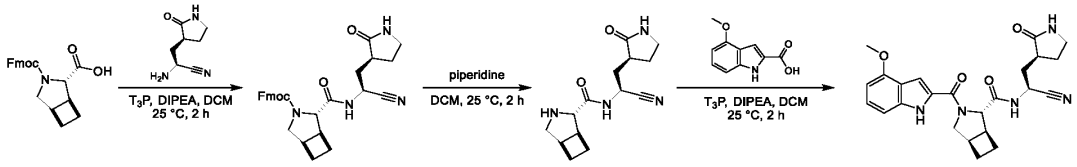
Step 6: (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide

[000635] A solution of (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide (100 mg, 219.54 umol, 1 eq) in DCM (5 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (313.90 mg, 1.32 mmol, 6 eq) was stirred at 20 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 * 30mm * 3um; mobile phase: [water (0.2% FA) - ACN]; B%: 25% - 60%, 8 min) to afford (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide (33 mg, 75.43 umol, 34.36% yield, 100% purity) as a white solid. MS (ESI) *m/z* 438.2 $[M+H]^+$.

[000636] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.73 - 11.47 (m, 1H), 8.85 (br d, J = 8.3 Hz, 1H), 7.84 - 7.54 (m, 1H), 7.24 - 6.84 (m, 3H), 6.74 - 6.48 (m, 1H), 5.10 - 4.47 (m, 2H), 4.20- 3.75 (m, 4H), 3.47 (t, J = 9.0 Hz, 1H), 3.16 (d, J = 7.9 Hz, 1H), 2.61 (s, 1H), 2.43 - 2.36 (m, 1H), 2.27 - 1.43 (m, 7H), 1.07 (d, J = 6.4 Hz, 3H).

[000637] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.25 - 6.75 (m, 3H), 6.59 - 6.40 (m, 1H), 5.15 - 5.00 (m, 1H), 4.84 - 4.61 (m, 1H), 4.30 - 4.06 (m, 1H), 3.98 - 3.84 (m, 3H), 3.55 (t, J = 8.9 Hz, 1H), 3.30 - 3.24 (m, 1H), 3.01 - 2.54 (m, 2H), 2.46 - 2.09 (m, 4H), 2.01 - 1.38 (m, 3H), 1.15 (br d, J = 6.6 Hz, 3H).

Example 64. Synthesis of viral protease inhibitor compound 547



Step 1: 9H-fluoren-9-ylmethyl (1S,2S,5R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-azabicyclo[3.2.0]heptane-3-carboxylate

[000638] (1S,2S,5R)-3-(9H-fluoren-9-ylmethoxycarbonyl)-3-azabicyclo[3.2.0]heptane-2-carboxylic acid (150 mg, 412.76 umol, 1 eq), (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanenitrile (75.87 mg, 495.31 umol, 1.2 eq) in DCM (2 mL) was added T3P (394.00 mg, 619.14 umol, 368.22 uL, 50% purity, 1.5 eq) and DIEA (160.04 mg, 1.24 mmol, 215.69 uL, 3 eq), and the resulting mixture was stirred at 25 °C for 2 h. Upon completion, the solution was diluted with H_2O (20 mL), extracted with ethyl acetate (20 mL * 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to afford 9H-fluoren-9-ylmethyl (1S,2S,5R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-azabicyclo[3.2.0]heptane-3-carboxylate (130 mg, 260.74 umol, 63.17% yield, 100% purity) as white solid. MS (ESI) *m/z* 499.3 $[M+H]^+$.

Step 2: (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-azabicyclo[3.2.0]heptane-2-carboxamide

[000639] To a solution of 9H-fluoren-9-ylmethyl (1S,2S,5R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-azabicyclo[3.2.0]heptane-3-carboxylate (250 mg, 401.15 umol, 80% purity, 1 eq) in DCM (2.5 mL) was added piperidine (68.31 mg, 802.29 umol, 79.23 uL, 2 eq), and the solution was stirred at 25 °C for 2 h. Upon completion, DCM was removed with blow-dry to afford a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-azabicyclo[3.2.0]heptane-2-carboxamide (80 mg, 289.51 umol, 72.17% yield, 100% purity) as yellow solid. MS (ESI) *m/z* 277.2 $[M+H]^+$.

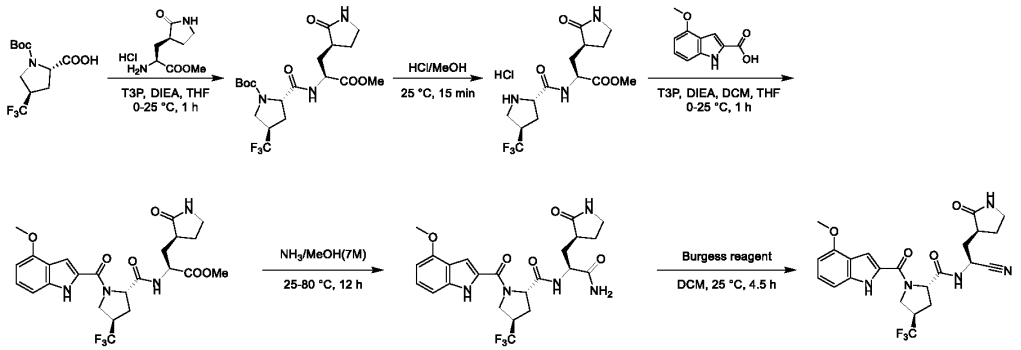
Step 3: (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.2.0]heptane-2-carboxamide

[000640] To a solution of (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-azabicyclo[3.2.0]heptane-2-carboxamide (80 mg, 289.51 umol, 1 eq), 4-

methoxy-1H-indole-2-carboxylic acid (83.02 mg, 434.26 umol, 1.5 eq) in DCM (1.5 mL) was added the T3P (276.35 mg, 434.26 umol, 258.27 uL, 50% purity, 1.5 eq) and DIEA (112.25 mg, 868.52 umol, 151.28 uL, 3 eq). The resulting solution was stirred at 25 °C for 1 h. Upon completion, the solution was diluted with H_2O (20 mL), extracted with ethyl acetate (20 mL * 3), and the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 20%-50%,8min) to afford (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.2.0]heptane-2-carboxamide (50 mg, 111.23 umol, 38.42% yield, 100% purity) as white solid. MS (ESI) *m/z* 449.9 $[M+H]^+$.

[000641] ^1H NMR (400MHz, DMSO-d_6) δ = 11.57 (br s, 1H), 9.23 - 8.65 (m, 1H), 7.69 (br s, 1H), 7.23 - 6.82 (m, 3H), 6.52 (br d, *J*=7.4 Hz, 1H), 5.08 - 4.84 (m, 1H), 4.63 (br d, *J*=8.2 Hz, 1H), 4.25 (br s, 1H), 4.06 (br s, 1H), 3.89 (br s, 3H), 3.27 - 2.79 (m, 4H), 2.28 - 1.53 (m, 9H).

Example 65. Synthesis of viral protease inhibitor compound 549



Step 1: tert-butyl (2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl] carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate

[000642] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (283.01 mg, 1.27 mmol, 1.2 *eq*, HCl) and (2S,4R)-1-tert-butoxycarbonyl-4-(trifluoromethyl)pyrrolidine-2-carboxylic acid (300 mg, 1.06 mmol, 1 *eq*), DIEA (684.44 mg, 5.30 mmol, 922.43 uL, 5 *eq*) in THF (3 mL) was added T3P (1.01 g, 1.59 mmol, 944.87 uL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 1 h.

Upon completion, the residue was poured into saturated sodium bicarbonate solution (10 mL) and stirred for 1 min. The aqueous phase was extracted with ethyl acetate (10 mL * 2). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give tert-butyl(2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate (0.5 g, crude) as light yellow oil and used directly next step. MS (ESI) *m/z* 452.1 $[M+H]^+$.

Step 2: methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(2S,4R)-4-(trifluoromethyl)pyrrolidine-2- carbonyl]amino]propanoate

[00643] To tert-butyl (2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl]carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate (0.5 g, 1.11 mmol, 1 *eq*) was added HCl/MeOH (4 M, 3 mL, 10.83 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 15 min. Upon completion, the reaction mixture was concentrated to get the crude product methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl] -2-[[(2S,4R)-4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]propanoate (450 mg, crude, HCl) as the light yellow oil. MS (ESI) *m/z* 352.1 $[M+H]^+$.

Step 3: methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2- carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[00644] To a mixture of methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(2S,4R)-4-(trifluoromethyl) pyrrolidine-2-carbonyl]amino]propanoate (395.52 mg, 1.02 mmol, 1.3 *eq*, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (150 mg, 784.59 umol, 1 *eq*) and DIPEA (507.01 mg, 3.92 mmol, 683.31 uL, 5 *eq*) in THF (3 mL) and DCM (3 mL) was added T3P (748.92 mg, 1.18 mmol, 699.93 uL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was poured into saturated sodium bicarbonate solution (5 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (5 mL * 2). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by prep-TLC (dichloromethane:methanol = 10:1, R_f = 0.43) to give Methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl) -4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, crude) was obtained as the light yellow solid. MS (ESI) *m/z* 525.2 $[M+H]^+$.

Step 4: (2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-(nitrosomethyl)-2-[(3S)-2-oxopyrr olidin-3-yl]ethyl]-4-(trifluoromethyl)pyrrolidine-2-carboxamide

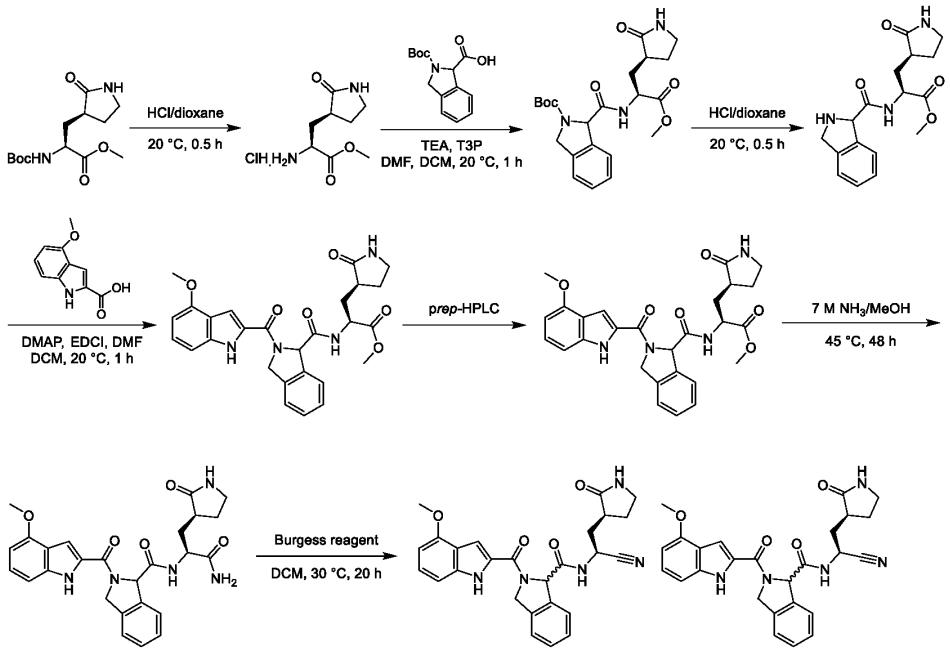
[000645] To a mixture of methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4- (trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 476.65 umol, 1 *eq*) was added NH_3/MeOH (7 M, 3 mL, 44.06 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was cooled to 25 °C and concentrated to get the crude product. The crude product was purified by prep-TLC (dichloromethane: methanol = 10:1, Rf = 0.3) to afford (2S,4R)-1-(4-methoxy- 1H-indole-2-carbonyl)-N-[(1S)-1-(nitrosomethyl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-(trifluoromethyl)pyrrolidine-2-carboxamide (130 mg, 247.51 umol, 51.93% yield, 97% purity) as a light yellow solid. MS (ESI) *m/z* 510.2 $[M+H]^+$.

Step 5: (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2- carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide

[000646] To a mixture of (2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-(nitrosomethyl)-2-[(3S) -2-oxopyrrolidin-3-yl]ethyl]-4-(trifluoromethyl)pyrrolidine-2-carboxamide (120 mg, 235.54 umol, 1 *eq*) in DCM (6 mL) was added Burgess reagent (112.26 mg, 471.07 umol, 2 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 4.5 h. Upon completion, the residue was poured into water (0.5 mL) and stirred for 10 min. Then the reaction mixture was concentrated to get the crude product. The crude product was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40mm*3um; mobile phase: [water (10mM NH_4HCO_3)-ACN];B%: 25%-45%,8min) to give (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopy rrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide (22.56 mg, 45.90 umol, 19.49% yield, 100% purity) as a white solid. MS (ESI) *m/z* 492.2 $[M+H]^+$.

[000647] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.12 - 7.21 (m, 1 H), 6.84 - 7.10 (m, 2 H), 6.50 (br s, 1 H), 4.94 - 5.26 (m, 1 H), 4.75 (br s, 1 H), 4.07 - 4.47 (m, 2 H), 3.79 - 4.01 (m, 3 H), 3.45 (br s, 1 H), 2.16 - 2.98 (m, 6 H), 1.62 - 2.02 (m, 2 H), 1.39 (br s, 1 H).

Example 66. Synthesis of viral protease inhibitor compound 557



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[000648] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.75 mmol, 1 *eq*) in HCl/dioxane (4 M, 8.73 mL, 20 *eq*) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 0.5 h under N_2 atmosphere. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (630 mg, crude, HCl) as a yellow oil. MS (ESI) *m/z* 223.2 $[M+H]^+$.

Step 2: tert-butyl 1-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)isoindoline-2-carboxylate

[000649] To a solution of 2-tert-butoxycarbonylisoindoline-1-carboxylic acid (436.93 mg, 1.66 mmol, 1 *eq*) methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (630 mg, 1.74 mmol, 61.58% purity, 1.05 *eq*, HCl) in DCM (5 mL) DMF (5 mL) was added T3P (1.58 g, 2.49 mmol, 1.48 mL, 50% purity, 1.5 *eq*) and TEA (1.01 g, 9.96 mmol, 1.39 mL, 6 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (20 mL), and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine 15 mL, dried over Na_2SO_4, filtered

and concentrated under reduced pressure to get the product tert-butyl 1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]isoindoline-2-carboxylate (720 mg, crude) as a white solid. MS (ESI) *m/z* 432.2 $[M+H]^+$.

Step 3:

(2S)-methyl 2-(isoindoline-1-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000650] A mixture of tert-butyl 1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]isoindoline-2-carboxylate (720 mg, 1.67 mmol, 1 *eq*) in HCl/dioxane (4 M, 8.34 mL, 20 *eq*) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 0.5 h under N_2 atmosphere. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product methyl (2S)-2-(isoindoline-1-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (770 mg, crude, HCl) as a brown oil. MS (ESI) *m/z* 332.3$[M+H]^+$.

Step 4:

(2S)-methyl 2-(2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000651] A mixture of 4-methoxy-1H-indole-2-carboxylic acid (287.43 mg, 1.50 mmol, 1 *eq*), methyl (2S)-2-(isoindoline-1-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (770 mg, 1.65 mmol, 79% purity, 1.1 *eq*, HCl), DMAP (367.34 mg, 3.01 mmol, 2 *eq*), EDCI (576.42 mg, 3.01 mmol, 2 *eq*) in DCM (8 mL) and DMF (2.7 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 1 h under N_2 atmosphere. Upon completion, the reaction mixture was quenched by addition H_2O (25 mL), and then extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by neutral *prep*-HPLC (column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-45%,10min) to afford methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (Isomer 1: 150mg, 297.30 umol, 19.78% yield) as white solid. MS (ESI) *m/z* 505.3$[M+H]^+$; and to afford methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (Isomer 2: 140 mg, 277.48 umol, 18.46% yield) as white solid. MS (ESI) m/z 505.3[M+H]+.

Step 5 N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide

[000652] A solution of methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 297.30 umol, 1 *eq*) in MeOH/NH_3 (7 M, 849.44 uL, 20 *eq*) was stirred at 45 °C for 48 h. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (130 mg, crude) as colorless oil. MS (ESI) *m/z* 490.3$[M+H]^+$.

Step 5 N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide

[000653] A solution of methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carbonyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (140 mg, 277.48 umol, 1 *eq*) in MeOH/NH_3 (7 M, 792.81 uL, 20 *eq*) was stirred at 45 °C for 24 h. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (110 mg, crude) as colorless oil. MS (ESI) *m/z* 490.3$[M+H]^+$.

Step 6 N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide

[000654] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (125 mg, 255.35 umol, 1 *eq*) in DCM (8 mL) was added Burgess reagent (273.84 mg, 1.15 mmol, 4.5 *eq*), and the resulting mixture was stirred at 30 °C for 20 h. Upon completion, the reaction mixture was quenched by addition H_2O (0.5 mL), and then concentrated under reduced pressure to give a residue. The residue was purified by neutral *prep*-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 20%-50%,10 min) to afford product N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (31.50 mg, 66.81 umol, 26.16% yield, 100% purity) as a white solid. MS (ESI) *m/z* 472.3$[M+H]^+$.

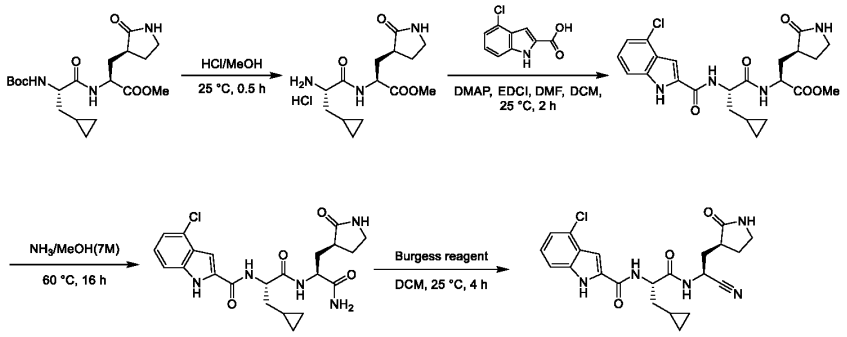
[000655] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.53 - 11.83 (m, 1 H) 9.11 - 9.78 (m, 1 H) 7.31 - 7.78 (m, 5 H) 6.95 - 7.29 (m, 3 H) 6.42 - 6.63 (m, 1 H) 5.73 (s, 1 H) 5.27 - 5.41 (m, 1 H) 4.91 - 5.05 (m, 1 H) 3.76 - 3.99 (m, 3 H) 2.71 - 3.19 (m, 2 H) 2.00 - 2.30 (m, 3 H) 1.20 - 1.87 (m, 2 H).

Step 6 N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide

[000656] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] -2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (105 mg, 214.49 umol, 1 *eq*) in DCM (6 mL) was added Burgess reagent (204.47 mg, 857.98 umol, 4 *eq*). The mixture was stirred at 30 °C for 7 h. Upon completion, the reaction mixture was quenched by addition H_2O (0.5 mL), and then concentrated under reduced pressure to give a residue. The residue was purified by neutral *prep*-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 25%-55%,8min) to afford N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (34.83 mg, 73.72 umol, 34.37% yield, 99.791% purity) as a white solid. MS (ESI) *m/z* 472.3$[M+H]^+$.

[000657] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.72 (s, 1 H) 9.19 (d, *J*=8.11 Hz, 1 H) 7.31 - 7.76 (m, 5 H) 6.92 - 7.29 (m, 3 H) 6.56 (d, *J*=7.75 Hz, 1 H) 5.74 (s, 1 H) 5.34 (br d, *J*=10.13 Hz, 1 H) 4.96 (q, *J*=8.23 Hz, 1 H) 3.86 - 3.89 (m, 1 H) 3.86 - 4.55 (m, 1 H) 3.84 - 4.01 (m, 3 H) 2.96 - 3.22 (m, 2 H) 2.25 - 2.41 (m, 1 H) 2.02 - 2.20 (m, 2 H) 1.47 - 1.87 (m, 2 H).

Example 67. Synthesis of viral protease inhibitor compound 647



[000658] A mixture of methyl 2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.3 g, 3.27 mmol, 1 *eq*) in HCl/MeOH (15 mL) was stirred at 25 °C for 30 min. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.3 g, crude) as a white solid.

Step 2: methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000659] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.68 mmol, 1 *eq*) in DCM (6 mL) and DMF (2 mL), the mixture was added DMAP (616.30 mg, 5.04 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added 4-chloro-1H-indole-2-carboxylic acid (394.69 mg, 2.02 mmol, 1.2 *eq*) and EDCI (967.04 mg, 5.04 mmol, 3 *eq*) and stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5/1 to ethyl acetate/methanol = 10/1) to give methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (760 mg, 1.60 mmol, 95.16% yield) as a white solid. MS (ESI) m/z 475.2 $[M+H]^+$.

Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-indole-2-carboxamide

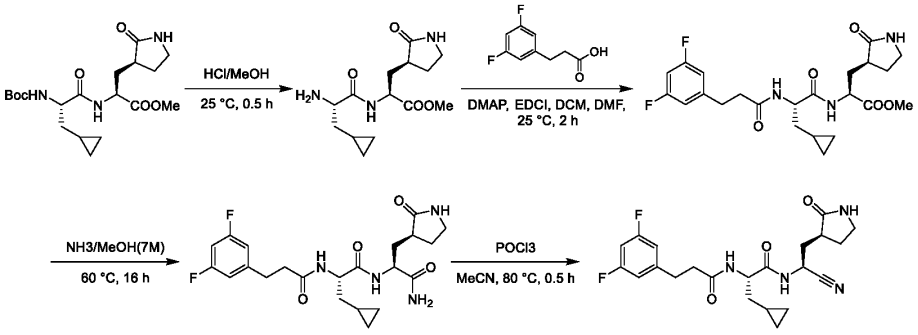
[000660] A mixture of methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (700 mg, 1.47 mmol, 1 *eq*) in NH_3/MeOH (7 M, 15 mL, 71.24 *eq*) was stirred at 60 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-indole-2-carboxamide (660 mg, 1.44 mmol, 97.36% yield) as a white solid. MS (ESI) m/z 460.2 $[M+H]^+$.

Step 4: 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000661] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-indole-2-carboxamide (630 mg, 1.37 mmol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (652.87 mg, 2.74 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition, column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-50%,8min) to give 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (110 mg, 248.92 umol, 18.17% yield) as a white solid. MS (ESI) m/z 442.2 $[M+H]^+$.

[000662] ^1H NMR (400MHz, DMSO-d_6) δ = 11.96 (br s, 1H), 8.93 (d, J=8.2 Hz, 1H), 8.76 (d, J=7.7 Hz, 1H), 7.78 - 7.67 (m, 1H), 7.46 - 7.36 (m, 2H), 7.21 - 7.09 (m, 2H), 5.04 - 4.89 (m, 1H), 4.55 - 4.43 (m, 1H), 3.12 (quin, J=9.3 Hz, 2H), 2.43 - 2.29 (m, 1H), 2.19 - 2.07 (m, 2H), 1.91 - 1.63 (m, 3H), 1.54 - 1.41 (m, 1H), 0.82 (br dd, J=5.6, 7.4 Hz, 1H), 0.50 - 0.34 (m, 2H), 0.26 - 0.04 (m, 2H).

Example 68. Synthesis of viral protease inhibitor compound 649



Step 1: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000663] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 968.64 umol, 77% purity, 1 *eq*) in HCl/MeOH (10 mL) was stirred at 25 °C for 30 min. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-

[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, crude) as a white solid.

Step 2: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[3-(3,5-difluorophenyl)propanoylamino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000664] A mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (288 mg, 968.56 umol, 1 *eq*) in DCM (5 mL) and DMF (2.5 mL) was added DMAP (354.98 mg, 2.91 mmol, 3 *eq*) and the mixture was added with 3-(3,5-difluorophenyl)propanoic acid (180.30 mg, 968.56 umol, 1 *eq*) and EDCI (928.37 mg, 4.84 mmol, 5 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (8 mL * 3). The combined organic layers were washed with brine (15 mL * 1), dried over with Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=5/1 to ethyl acetate/methanol=5:1) to give methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[3-(3,5-difluorophenyl)propanoylamino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 547.81 umol, 56.56% yield, 85% purity) as a white solid. MS (ESI) *m/z* 466.2 $[M+H]^+$.

Step 3: (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-3-cyclopropyl-2-[3-(3,5-difluorophenyl)propanoylamino]propanamide

[000665] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[3-(3,5-difluorophenyl)propanoylamino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 644.48 umol, 1 *eq*) in NH_3/methanol (7 M, 5.45 mL, 59.24 *eq*) was stirred at 60 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-3-cyclopropyl-2-[3-(3,5-difluorophenyl)propanoylamino]propanamide (260 mg, 577.16 umol, 89.55% yield) as a white solid. MS (ESI) *m/z* 451.2 $[M+H]^+$.

Step 4: (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[3-(3,5-difluorophenyl)propanoylamino]propanamide

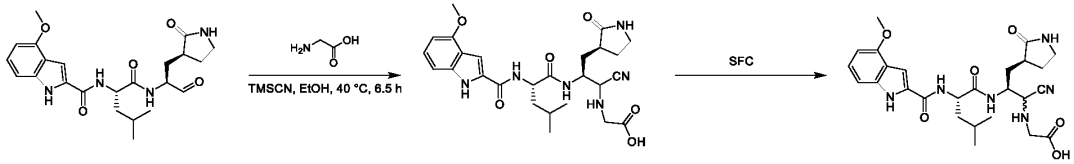
[000666] To a mixture of (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-3-cyclopropyl-2-[3-(3,5-difluorophenyl)propanoylamino]propanamide

(70 mg, 155.39 umol, 1 *eq*) in ACN (1 mL) was added $POCl_3$ (47.65 mg, 310.78 umol, 28.88 uL, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 80 °C for 0.5 h. Upon completion, the reaction mixture was quenched by addition $NaHCO_3$ (1 mL) at 25 °C, and then extracted with ethyl acetate (1 mL * 3). The combined organic layers were concentrated under reduced pressure to give crude product. The crude was purified by prep-HPLC (neutral condition, column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 20%-50%,8min) to give (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[3-(3,5-difluorophenyl)propanoylamino]propanamide (7 mg, 16.19 umol, 10.42% yield) as a white solid. MS (ESI) *m/z* 433.2 $[M+H]^+$.

[000667] ^1H NMR (400MHz, DMSO-d_6) δ = 9.09 - 8.81 (m, 1H), 8.15 (br d, *J*=7.5 Hz, 1H), 7.83 - 7.70 (m, 1H), 7.10 - 6.89 (m, 3H), 4.99 - 4.83 (m, 1H), 4.33 - 4.19 (m, 1H), 3.19 - 3.04 (m, 2H), 2.89 - 2.78 (m, 2H), 2.46 (br s, 2H), 2.39 - 2.03 (m, 3H), 1.84 - 1.46 (m, 3H), 1.40 - 1.19 (m, 1H), 0.59 (br s, 1H), 0.34 (br s, 2H), 0.14 -0.05 (m, 2H).

[000668] ^1H NMR (400MHz, METHANOL-d_4) δ = 6.84 (br t, *J*=5.7 Hz, 2H), 6.74 (tt, *J*=2.2, 9.3 Hz, 1H), 5.06 - 4.92 (m, 1H), 4.37 - 4.22 (m, 1H), 3.38 - 3.32 (m, 2H), 2.97 - 2.88 (m, 2H), 2.71 - 2.57 (m, 2H), 2.54 - 2.10 (m, 3H), 2.01 - 1.77 (m, 2H), 1.76 - 1.58 (m, 1H), 1.55 - 1.36 (m, 1H), 0.72 - 0.59 (m, 1H), 0.53 - 0.36 (m, 2H), 0.18 - 0.02 (m, 2H).

Example 69. Synthesis of viral protease inhibitor compound 653



[000669] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl -butyl]-4-methoxy-1H-indole-2-carboxamide (1 g, 1.81 mmol, 80% purity, 1 eq) in EtOH (20 mL) was added 2-aminoacetic acid (271.74 mg, 3.62 mmol, 20.52 uL, 2 eq), $ZnCl_2$ (1 M, 18.10 uL, 0.01 eq). The mixture was stirred at 25 °C for 30 min, and then TMSCN (359.14 mg, 3.62 mmol, 452.89 uL, 2 eq) was added and the resulting mixture was stirred at 40 °C for 6 h. Upon the reaction was completed,

the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by HCl prep-HPLC (column: Phenomenex luna C18 80*40mm*3 um; mobile phase: [water (0.04%HCl)-ACN]; B%: 25%-45%, 7 min) to get the mixture product 400 mg. The mixture was separated by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [Neu-ETOH]; B%: 50%-50%, 10 min) to get the compound 2-[[(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino] -3-[(3S)-2-oxopyrrolidin-3-yl]propyl]amino]acetic acid (125 mg, 235.87 umol, 13.03% yield, 99.363% purity) and 2-[[(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl -pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propyl]amino]acetic acid (205 mg, 373.82 umol, 20.65% yield, 96.023% purity) as a white solid. MS (ESI) *m/z* 527.3 $[M+H]^+$.

[000670] Isomer 1: ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.56 (d, *J*=2.0 Hz, 1H), 8.52 - 8.21 (m, 2H), 7.58 (s, 1H), 7.35 (d, *J*=1.7 Hz, 1H), 7.14 - 7.05 (m, 1H), 7.03 - 6.97 (m, 1H), 6.50 (d, *J*=7.7 Hz, 1H), 4.57 - 4.41 (m, 1H), 4.14 (tdd, *J*=4.2, 8.2, 12.2 Hz, 1H), 3.97 - 3.82 (m, 4H), 3.52 - 3.36 (m, 2H), 3.18 - 2.98 (m, 2H), 2.41 - 2.27 (m, 1H), 2.12 - 2.04 (m, 2H), 1.82 - 1.36 (m, 5H), 0.91 (dd, *J*=6.4, 15.8 Hz, 6H)

[000671] Isomer 2: ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.57 (d, *J*=2.0 Hz, 1H), 8.39 (d, *J*=7.8 Hz, 1H), 8.20 (d, *J*=9.5 Hz, 1H), 7.54 (s, 1H), 7.37 (d, *J*=1.6 Hz, 1H), 7.16 - 6.94 (m, 2H), 6.50 (d, *J*=7.6 Hz, 1H), 4.53 - 4.36 (m, 1H), 4.18 - 4.01 (m, 1H), 3.88 (s, 3H), 3.77 (d, *J*=8.8 Hz, 1H), 3.43 - 3.33 (m, 2H), 3.15 - 2.96 (m, 2H), 2.38 - 2.25 (m, 1H), 2.08 - 2.01 (m, 1H), 1.91 - 1.47 (m, 6H), 0.91 (dd, *J*=6.4, 14.8 Hz, 6H)

[000672] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl] -3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (700 mg, 1.27 mmol, 80% purity, 1 eq) in EtOH (10 mL) was added pyrrolidine (180.01 mg, 2.53 mmol, 211.28 uL, 2 eq), ZnCl2 (1 M, 12.66 uL, 0.01 eq), and the resulting mixture was stirred at 25 °C for 30 min. After the addition of TMSCN (251.10 mg, 2.53 mmol, 316.65 uL, 2 eq), the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC to afford N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2-pyrrolidin-1-yl-ethyl]carbamoyl]-3-methyl-butyl]-4-

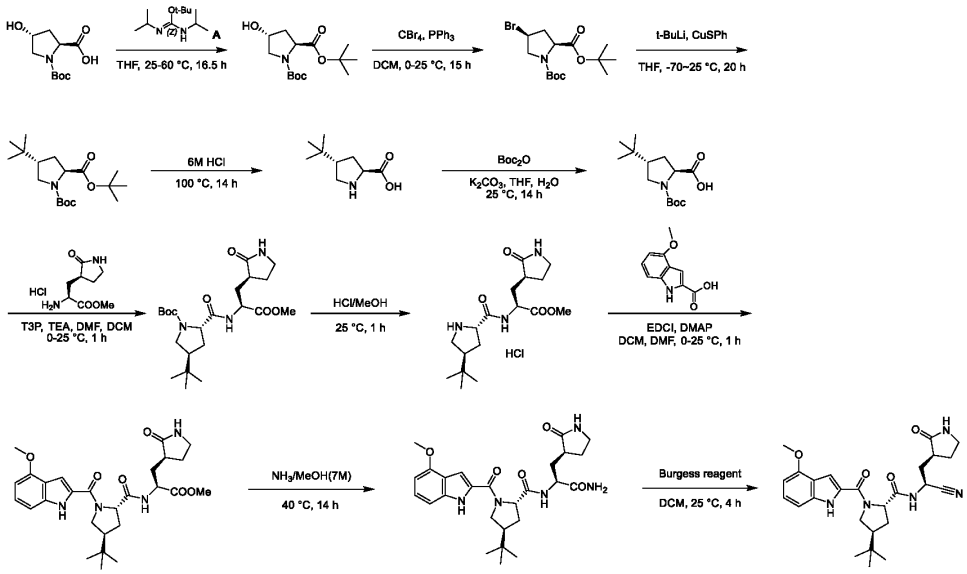
methoxy-1H-indole-2-carboxamide (110 mg, 199.95 umol, 15.80% yield, 95% purity) and N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2-pyrrolidin-1-yl-ethyl] carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (110 mg, 199.95 umol, 15.80% yield, 95% purity) as a white solid. MS (ESI) *m/z* 523.4 $[M+H]^+$

[000673] column: Phenomenex luna CN 5u 100*30mm;mobile phase: [Hexane-IPA];B%: 5%-40%,20min

[000674] Isomer 1: ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.58 (s, 1H), 8.43 (d, *J*=7.7 Hz, 1H), 8.20 (d, *J*=9.4 Hz, 1H), 7.68 - 7.49 (m, 1H), 7.38 (d, *J*=1.2 Hz, 1H), 7.18 - 6.93 (m, 2H), 6.50 (d, *J*=7.6 Hz, 1H), 4.57 - 3.99 (m, 3H), 3.88 (s, 3H), 3.19 - 2.95 (m, 2H), 2.64 - 2.53 (m, 4H), 2.38 - 2.27 (m, 1H), 2.15 - 2.01 (m, 1H), 1.85 - 1.44 (m, 10H), 0.91 (dd, *J*=6.4, 16.3 Hz, 6H)

[000675] Isomer 2: ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.59 (br s, 1H), 8.39 (br d, *J*=7.6 Hz, 1H), 8.01 (br d, *J*=9.1 Hz, 1H), 7.69 - 7.49 (m, 1H), 7.43 - 7.28 (m, 1H), 7.16 - 6.86 (m, 2H), 6.50 (d, *J*=7.6 Hz, 1H), 4.59 - 4.24 (m, 3H), 3.88 (s, 3H), 3.19 - 2.94 (m, 2H), 2.71 - 2.57 (m, 2H), 2.49 - 2.32 (m, 3H), 2.18 - 2.08 (m, 1H), 2.06 - 1.93 (m, 1H), 1.83 - 1.37 (m, 9H), 0.90 (dd, *J*=6.5, 15.2 Hz, 6H)

Example 70. Synthesis of viral protease inhibitor compound 655



Step 1: (2S,4R)-di-tert-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate

[000676] To a solution of (2S,4R)-1-tert-butoxycarbonyl-4-hydroxy-pyrrolidine-2-carboxylic acid (5 g, 21.62 mmol, 1 *eq*) in THF (75 mL) was added 2-tert-butyl-1,3-diisopropyl-isourea (6.50 g, 32.43 mmol, 1.5 *eq*) at 25 °C, and then the resulting solution was stirred at 60 °C for 2.5 h. 2-tert-butyl-1,3-diisopropyl-isourea (6.50 g, 32.43 mmol, 1.5 eq) was added to the mixture and then stirred at 60 °C for 14 h. Upon completion, the reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give (2S,4R)-di-tert-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate (4.3 g, 14.22 mmol, 65.75% yield, 95% purity) as a colorless oil. MS (ESI) *m/z* 288.2 $[M+H]^+$

Step 2: (2S,4S)-di-tert-butyl 4-bromopyrrolidine-1,2-dicarboxylate

[000677] To a solution of (2S,4R)-di-tert-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate (4 g, 13.92 mmol, 1 *eq*) in DCM (40 mL) was added CBr_4 (14.08 g, 42.46 mmol, 3.05 *eq*) at 25 °C. The mixture was cooled to 0 °C, and PPh_3 (11.32 g, 43.15 mmol, 3.1 *eq*) was added carefully. The reaction was stirred at 25 °C for 15 h. Upon completion, ethanol (4 mL) was added, and the solution was stirred for 2 h. MTBE (40 mL) was added dropwise to precipitate the phosphine oxide, which was filtered off, the filter cake was washed with DCM (30 mL* 2), and the filtrate was concentrated under reduced pressure to give a brown oil. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 100:0 to 10:1) to give (2S,4S)-di-tert-butyl 4-bromopyrrolidine-1,2-dicarboxylate (1.5 g, 4.07 mmol, 29.23% yield, 95% purity) as light yellow oil.

Step 3: (2S,4S)-di-tert-butyl 4-(tert-butyl)pyrrolidine-1,2-dicarboxylate

[000678] A mixture of phenylsulfanylcopper (1.58 g, 9.14 mmol, 6.4 *eq*) in dry THF (30 mL) was cooled to -70 °C, and then treated with careful addition of t-BuLi (1.3 M, 7.03 mL, 6.4 *eq*). The resulting mixture was stirred for 30 min, and a precooled (-20 °C) solution of (2S,4S)-di-tert-butyl 4-bromopyrrolidine-1,2-dicarboxylate (500 mg, 1.43 mmol, 1 *eq*) in dry THF (5 mL) was added. The reaction was stirred at -70 °C for 5 h, and then warmed to 25 °C for 15 h under N_2. Upon completion, the reaction was quenched by pouring into a solution of saturated aqueous NH_4Cl (30 mL). The aqueous mixture was stirred vigorously for 30 min. Solids were filtered off, and the phases were separated. The aqueous phase was extracted with MTBE (10 mL* 3), and the combined organic phases

were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated under reduced pressure to give a crude. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 100:0 to 10:1) to give (2S,4S)-di-tert-butyl 4-(tert-butyl)pyrrolidine-1,2-dicarboxylate (290 mg, 797.05 umol, 55.83% yield, 90% purity) as an off-white solid.

Step 4: (2S,4S)-4-(tert-butyl)pyrrolidine-2-carboxylic acid

[000679] A mixture of (2S,4S)-di-tert-butyl 4-(tert-butyl)pyrrolidine-1,2-dicarboxylate (250 mg, 763.46 umol, 1 *eq*) in HCl (6 M, 2.5 mL, 19.65 *eq*) was stirred at 100 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S,4S)-4-tert-butylpyrrolidine-2-carboxylic acid (158 mg, crude, HCl) as a yellow solid.

Step 5: (2S,4S)-1-(tert-butoxycarbonyl)-4-(tert-butyl)pyrrolidine-2-carboxylic acid

[000680] To a mixture of (2S,4S)-4-tert-butylpyrrolidine-2-carboxylic acid (158 mg, 760.72 umol, 1 *eq*, HCl) in THF (1 mL) and H_2O (1 mL) was added K_2CO_3 (315.41 mg, 2.28 mmol, 3 *eq*) and Boc_2O (199.23 mg, 912.87 umol, 209.72 uL, 1.2 *eq*). The reaction was stirred at 25 °C for 14 h under N_2. Upon completion, the reaction mixture was concentrated under reduced pressure to afford (2S,4S)-1-(tert-butoxycarbonyl)-4-(tert-butyl)pyrrolidine-2-carboxylic acid (650 mg, crude) as a yellow solid.

Step 6: (2S,4S)-tert-butyl 4-(tert-butyl)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate

[000681] To a solution of (2S,4S)-1-(tert-butoxycarbonyl)-4-(tert-butyl)pyrrolidine-2-carboxylic acid (630 mg, 696.51 umol, 30% purity, 1 *eq*) in DCM (6 mL) and DMF (3 mL) was added TEA (422.88 mg, 4.18 mmol, 581.68 uL, 6 *eq*), methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (186.11 mg, 835.82 umol, 1.2 *eq*, HCl). After adding T3P (1.33 g, 2.09 mmol, 1.24 mL, 50% purity, 3 *eq*) at 0 °C, the mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was quenched with water (10.0 mL) and extracted with DCM (10.0 mL * 3). The organic layers were washed with brine (10.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 10:1 to 0:1) to afford *tert-butyl (2S,4S)-tert-butyl 4-(tert-butyl)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-*

carboxylate (240 mg, 546.02 umol, 78.39% yield) as yellow solid. MS (ESI) *m/z* 440.3 $[M+H]^+$.

Step 7: (S)-methyl 2-((2S,4S)-4-(tert-butyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000682] A solution of tert-butyl (2S,4S)-tert-butyl 4-(tert-butyl)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (230 mg, 523.27 umol, 1 eq) in HCl/MeOH (4 M, 2.3 mL, 17.58 eq) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (S)-methyl 2-((2S,4S)-4-(tert-butyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (196 mg, crude, HCl) as a light yellow solid. MS (ESI) m/z 340.2 $[M+H]^+$.

Step 8: (S)-methyl 2-((2S,4S)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000683] To a solution of (S)-methyl 2-((2S,4S)-4-(tert-butyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (196 mg, 521.43 umol, 1 *eq*, HCl) in DCM (2 mL) and DMF (1 mL) was added 4-methoxy-1H-indole-2-carboxylic acid (99.69 mg, 521.43 umol, 1 *eq*), DMAP (127.41 mg, 1.04 mmol, 2 *eq*), and then EDCI (199.92 mg, 1.04 mmol, 2 *eq*) at 0 °C. The mixture was then stirred at 25 °C for 1 h. Upon completion, the mixture was quenched with water (10.0 mL) and extracted with DCM (10 mL * 3). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, dichloromethane: methanol = 10:1 to 4:1) to give (S)-methyl 2-((2S,4S)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (250 mg, 414.56 umol, 79.50% yield, 85% purity) as a yellow solid. MS (ESI) *m/z* 513.3 $[M+H]^+$.

Step 9: (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[000684] A solution of (S)-methyl 2-((2S,4S)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (235 mg, 389.68 umol, 85% purity, 1 *eq*) in NH_3/methanol (7 M, 5 mL) was stirred at 40 °C for 14

h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (193 mg, crude) as a yellow solid. MS (ESI) *m/z* 498.3 $[M+H]^+$.

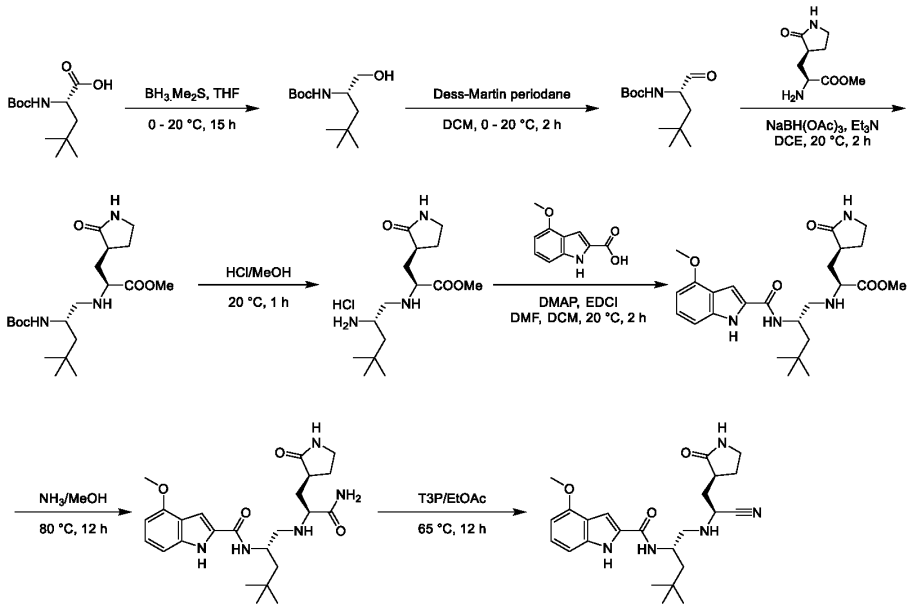
Step 10: (2S,4S)-4-(tert-butyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[000685] To a solution of (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (193 mg, 329.69 umol, 85% purity, 1 *eq*) in DCM (3 mL) was added Burgess reagent (235.71 mg, 989.08 umol, 3 *eq*), and then was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-55%,10min) to give (2S,4S)-4-(tert-butyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (59.58 mg, 124.24 umol, 37.68% yield, 100% purity) as a white solid. MS (ESI) *m/z* 480.2 $[M+H]^+$.

[000686] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.69 - 11.55 (m, 1H), 9.17 - 8.75 (m, 1H), 7.81 - 7.44 (m, 1H), 7.16 - 7.07 (m, 1H), 7.06 - 6.98 (m, 2H), 6.55 - 6.46 (m, 1H), 5.03 - 4.53 (m, 2H), 4.04 - 3.74 (m, 4H), 3.69 - 3.36 (m, 1H), 3.22 - 2.55 (m, 2H), 2.35 - 1.95 (m, 5H), 1.83 - 1.51 (m, 3H), 1.00 - 0.82 (m, 9H).

[000687] ^{1}H NMR (400MHz, DMSO-d_6, 273+80K) δ = 11.31 (s, 1H), 8.68 (s, 1H), 7.38 (s, 1H), 7.18 - 7.02 (m, 2H), 6.90 (s, 1H), 6.60 - 6.47 (m, 1H), 4.96 (q, *J*=7.6 Hz, 1H), 4.72 (s, 1H), 4.07 - 3.80 (m, 4H), 3.66 - 3.50 (m, 1H), 3.28 - 3.05 (m, 2H), 2.32 - 1.97 (m, 5H), 1.95 - 1.64 (m, 3H), 0.95 (s, 9H).

Example 71. Synthesis of viral protease inhibitor compound 659



Step 1: (S)-tert-butyl (1-hydroxy-4,4-dimethylpentan-2-yl)carbamate

[000688] To a solution of (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (5 g, 20.38 mmol, 1 eq) in THF (100 mL) at 0 °C, BH_3-Me_2S (10 M, 4.08 mL, 2.0 eq) was added drop-wise slowly, then the mixture was stirred at 20 °C for 15 h. The reaction mixture was added into MeOH (40 mL) and stirred for 20 min, then the mixture was concentrated. The residue was diluted with aq. $NaHCO_3$ (150 mL) and extracted with DCM (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 1:0 to 1:1) to afford tert-butyl N-[(1S)-1-(hydroxymethyl)-3,3-dimethyl-butyl]carbamate (2.5 g, 10.81 mmol, 53.02% yield) as a colorless oil.

Step 2: (S)-tert-butyl (4,4-dimethyl-1-oxopentan-2-yl)carbamate

[000689] To a solution of tert-butyl N-[(1S)-1-(hydroxymethyl)-3,3-dimethyl-butyl]carbamate (2.4 g, 10.37 mmol, 1 eq) in DCM (40 mL) was added periodinane (5.72 g, 13.49 mmol, 4.18 mL, 1.3 eq) via Dess-martin at 0 °C, and the reaction was stirred for 1 h. The mixture was warm to 20 °C and stirred for 1 h. The reaction mixture was quenched by addition H_2O (60 mL) at 0 °C, and then added drop-wise aq. $NaHCO_3$ to pH = 8 at 0 °C, and extracted with EtOAc (40 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced

pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1 to 1:1) to afford tert-butyl N-[(1S)-1-formyl-3,3-dimethyl-butyl]carbamate (1.6 g, 6.98 mmol, 67.25% yield) as a colorless oil.

[000690] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.40 (s, 1 H) 7.30 (br d, *J*=8.00 Hz, 1 H) 3.91 - 3.82 (m, 1 H) 1.66 (dd, *J*=14.38, 2.75 Hz, 1 H) 1.39 (s, 9 H) 1.32 (br d, *J*=9.26 Hz, 1 H) 0.90 (s, 9 H).

Step 3: (S)-methyl2-(((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000691] To a solution of *tert*-butyl N-[(1S)-1-formyl-3,3-dimethyl-butyl]carbamate (0.8 g, 3.49 mmol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.17 g, 5.23 mmol, 1.5 eq, HCl) in DCE (20 mL) was added Et_3N (529.52 mg, 5.23 mmol, 728.36 uL, 1.5 eq) and $NaBH(OAc)_3$ (2.22 g, 10.47 mmol, 3 eq), and the reaction was stirred at 20 °C for 2 h.

[000692] The reaction mixture was quenched by addition aq. $NaHCO_3$ (100 mL) at 0 °C and stirred for 0.5 h, then extracted with DCM (60 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1 to 1:3) to get the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (450 mg, 1.13 mmol, 32.29% yield) as a white solid. MS (ESI) *m/z* 400.3 $[M+H]^+$.

Step 4: (S)-methyl 2-(((S)-2-amino-4,4-dimethylpentyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000693] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 500.60 umol, 1 eq) in HCl/MeOH (4 M, 4.00 mL, 31.96 eq) was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (168 mg, crude, HCl) as a white solid.

Step 5: (S)-methyl 2-(((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000694] To a solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (168 mg, 500.20 umol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (95.63 mg, 500.20 umol, 1 eq) in DMF (1 mL) was added DMAP (183.32 mg, 1.50 mmol, 3.0 eq) and EDCI (191.78 mg, 1.00 mmol, 2 eq) and DCM (3 mL), the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition H_2O 40 mL at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 1:0 to 0:1) to afford methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 301.54 umol, 60.28% yield, 95% purity) as a yellow oil. MS (ESI) *m/z* 473.2 $[M+H]^+$.

Step 6: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4,4-dimethylpentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000695] A solution of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (130 mg, 275.09 umol, 1 eq) in NH_3/MeOH (7 M, 15 mL, 381.70 eq) was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, ethyl acetate:methanol = 50:3) to get the product N-[(1S)-1-[[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]methyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (60 mg, 131.13 umol, 47.67% yield) as a yellow solid. MS (ESI) *m/z* 458.3 $[M+H]^+$.

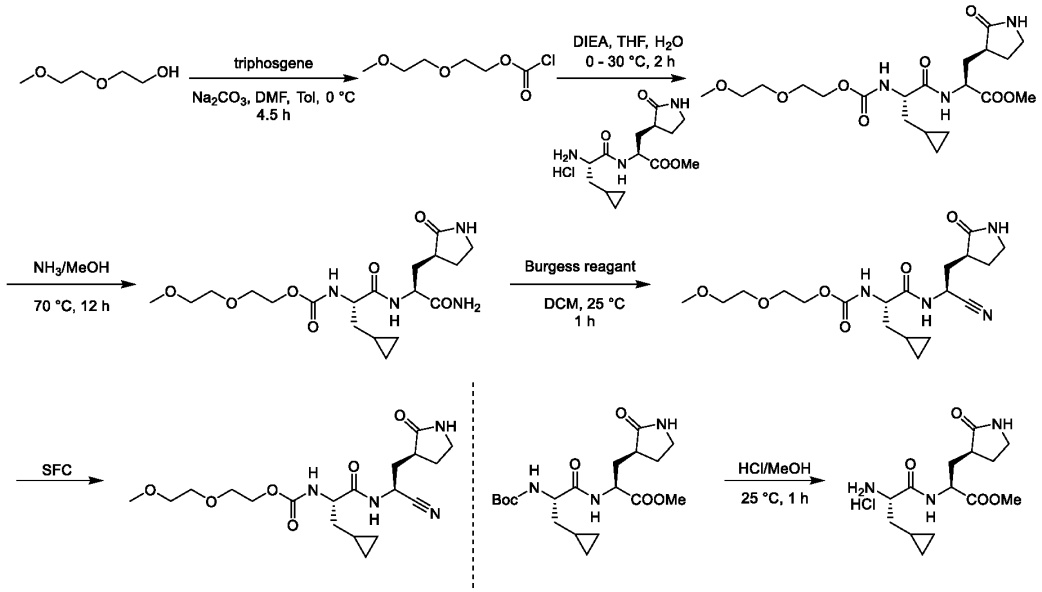
Step 7: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-4,4-dimethylpentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000696] To a solution of N-[(1S)-1-[[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]methyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (50 mg, 109.27 umol, 1 eq) in EtOAc (2 mL) was added T_3P (2.14 g, 3.36 mmol, 2 mL, 50% purity, 30.77 eq) drop-wise, and then the mixture was stirred at 65 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue

was purified by prep-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 um; mobile phase: [water (0.2% FA) - ACN]; B%: 15% - 45%, 8 min) and was separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um);mobile phase: [0.1% NH_3H_2O ETOH]; B%: 25% - 25%, 20 min) to afford N-[(1S)-1-[[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]methyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (4.4 mg, 9.92 umol, 29.07% yield, 99.1% purity) as a white solid. MS (ESI) *m/z* 440.2 $[M+H]^+$.

[000697] ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.22 - 6.99 (m, 3 H) 6.52 (br d, *J*=7.72 Hz, 1 H) 4.74 - 4.65 (m, 1 H) 4.61 - 4.48 (m, 1 H) 4.03 - 3.91 (m, 4 H) 3.62 - 3.51 (m, 1 H) 3.47 - 3.36 (m, 1 H) 3.27 - 3.19 (m, 1 H) 2.50 - 2.41 (m, 1 H) 2.29 - 2.18 (m, 1 H) 1.81 (br s, 1 H) 1.74 - 1.64 (m, 2 H) 1.60 (br d, *J*=10.14 Hz, 1 H) 1.34 - 1.28 (m, 1 H) 0.98 (s, 9 H).

Example 72. Synthesis of viral protease inhibitor compound 671



Step 1: 2-(2-methoxyethoxy)ethyl carbonochloridate

[000698] A mixture of triphosgene (4.93 g, 16.61 mmol, 4.99e-1 eq), Na_2CO_3 (3.53 g, 33.29 mmol, 1 eq) and DMF (95.00 mg, 1.30 mmol, 0.1 mL, 3.90e-2 eq) in toluene (50

mL) was cooled to 0 °C and stirred for 0.5 h under N_2 atmosphere. Then a solution of 2-(2-methoxyethoxy)ethanol (4 g, 33.29 mmol, 3.92 mL, 1 eq) was added dropwise. The mixture was stirred at 0 °C for 4 h. Upon completion, the mixture was filtered, and the filtrate was concentrated under the reduced pressure affording 2-(2-methoxyethoxy)ethyl carbonochloridate (6 g) as a yellow oil.

Step 2: (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000699] A mixture of methyl(2*S*)-2-[[(2*S*)-2-(*tert*-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (600 mg, 1.51 mmol, 1 eq) was in HCl/MeOH (4 M, 12.00 mL, 31.80 eq) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure affording methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (450 mg) as a white solid.

Step 3: (11S,14S)-methyl11-(cyclopropylmethyl)-9,12-dioxo-14-(((S)-2-oxopyrrolidin-3-yl)methyl)-2,5,8-trioxa-10,13-diazapentadecan-15-oate

[000700] To a solution of methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (450 mg, 1.51 mmol, 1 eq) in THF (10 mL) and H_2O (1 mL) was added DIEA (391.19 mg, 3.03 mmol, 527.20 uL, 2 eq), and then 2-(2-methoxyethoxy)ethyl carbonochloridate (414.52 mg, 2.27 mmol, 1.5 eq) was added at 0 °C. The mixture was stirred at 30 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (100 mL), and then extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250 * 50 mm * 10 um); mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 1% - 25%, 10 min) affording methyl(2*S*)-2-[[(2*S*)-3-cyclopropyl-2-[2-(2-methoxyethoxy)ethoxycarbonylamino]propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (400 mg, 901.94 umol, 59.60% yield) as a yellow oil. MS (ESI) *m/z* 444.2 $[M+H]^+$.

Step 4: 2-(2-methoxyethoxy)ethyl((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate

[000701] A mixture of methyl(2*S*)-2-[[(2*S*)-3-cyclopropyl-2-[2-(2-methoxyethoxy)ethoxycarbonylamino]propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (400 mg, 901.94 umol, 1 eq) in NH_3/MeOH (7 M, 10 mL, 77.61 eq) was stirred at 70 °C for 12 h. Upon completion, the mixture was concentrated under the reduced pressure to afford 2-(2-methoxyethoxy)ethyl*N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (400 mg, crude) as a yellow oil. MS (ESI) *m/z* 429.2 $[M+H]^+$

Step 5: 2-(2-methoxyethoxy)ethyl((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate

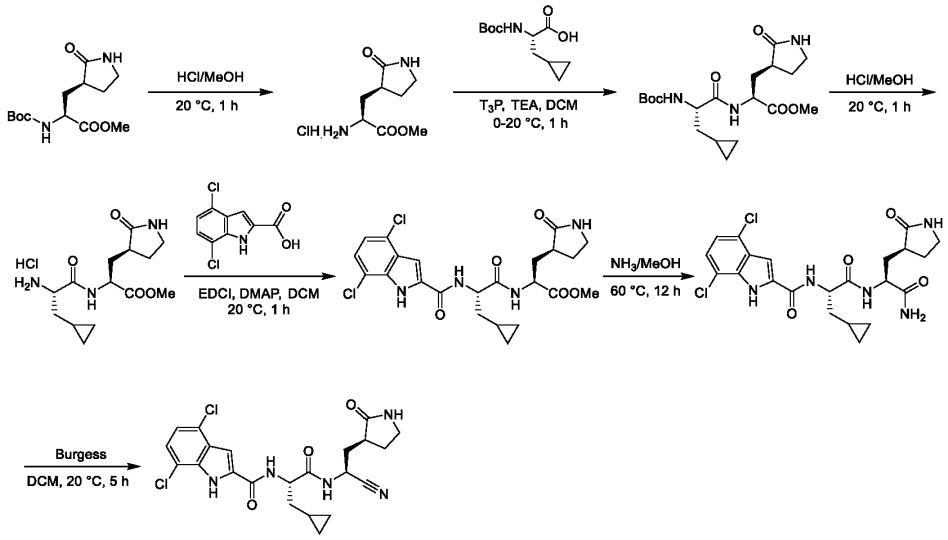
[000702] To a solution of 2-(2-methoxyethoxy)ethyl *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (380 mg, 886.86 umol, 1 eq) in DCM (5 mL) was added Burgess reagent (422.69 mg, 1.77 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (50 mL), and extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified with prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 10% - 40%, 8 min) affording 2-(2-methoxyethoxy)ethyl *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (150 mg, crude) as a white solid. MS (ESI) *m/z* 411.2 $[M+H]^+$

Step 6: 2-(2-methoxyethoxy)ethyl((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate

[000703] 2-(2-methoxyethoxy)ethyl*N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (150 mg, crude) was separated by SFC (column: DAICEL CHIRALPAK AD(250 mm * 30 mm, 10 um); mobile phase: [Neu-EtOH]; B%: 44% - 44%, 8 min) affording 2-(2-methoxyethoxy)ethyl *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (110 mg, 262.36 umol, 71.79% yield, 97.9% purity) as a colorless gum. MS (ESI) *m/z* 411.2 $[M+H]^+$.

[000704] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.81 (br d, J = 7.8 Hz, 1H), 7.72 (s, 1H), 7.54 (br d, J = 7.4 Hz, 1H), 4.95 (q, J = 8.2 Hz, 1H), 4.08 - 3.86 (m, 3H), 3.53 (td, J = 4.6, 15.2 Hz, 4H), 3.47 - 3.39 (m, 2H), 3.33 (s, 3H), 3.19 - 3.05 (m, 2H), 2.41 - 2.28 (m, 1H), 2.19 - 2.03 (m, 2H), 1.81 - 1.59 (m, 3H), 1.28 (td, J = 6.8, 13.6 Hz, 1H), 0.74 (br d, J = 5.6 Hz, 1H), 0.46 - 0.33 (m, 2H), 0.18 - 0.01 (m, 2H).

Example 73. Synthesis of viral protease inhibitor compound 691



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000705] A mixture of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (13.00 g, 45.40 mmol, 1 *eq*) and HCl/MeOH (4 M, 35 mL, 3.08 *eq*) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to afford methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (10 g, crude, HCl) was obtained as white solid. MS (ESI) *m/z* 223.1 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000706] A solution of methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (9.71 g, 43.62 mmol, 1 *eq*, HCl), (2*S*)-2-(*tert*-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (10 g, 43.62 mmol, 1 *eq*) and TEA (22.07 g, 218.08 mmol, 30.35 mL, 5 *eq*) in DCM (100 mL) was cooled to 0 °C, and then T3P (83.27 g, 130.85 mmol, 77.82

mL, 50% purity, 3 *eq*) was added into the solution. The mixture was stirred for 1 h and warmed to 20 °C gradually. Upon completion, the mixture was added H_2O (100 mL) and then extracted with ethyl acetate (100 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Then the residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1) to afford methyl(2*S*)-2-[[(2*S*)-2-(*tert*-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (12 g, 23.41 mmol, 53.67% yield, 77.53% purity) as a white solid. MS (ESI) *m/z* 398.2 $[M+H]^+$.

Step 3: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000707] A mixture of methyl (2*S*)-2-[[(2*S*)-2-(*tert*-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (1.5 g, 3.77 mmol, 1 *eq*) in HCl/methanol (4 M, 100 mL, 105.99 *eq*) was stirred at 20 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (1.1 g, crude, HCl) as a white solid. MS (ESI) *m/z* 298.2 $[M+H]^+$.

Step 4: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,7-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000708] A mixture of 4,7-dichloro-1H-indole-2-carboxylic acid (650 mg, 2.83 mmol, 1 *eq*), methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (943.18 mg, 2.83 mmol, 1 *eq*, HCl), EDCI (1.08 g, 5.65 mmol, 2 *eq*) and DMAP (1.04 g, 8.48 mmol, 3 *eq*) in DCM (10 mL) was stirred at 20 °C for 1 h. Upon completion, the mixture was added H_2O (50 mL) and then extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1) to afford methyl (2*S*)-2-[[(2*S*)-3-cyclopropyl-2-[(4,7-dichloro-1*H*-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (550 mg, 1.01 mmol, 35.92% yield, 93.99% purity) as a white solid. MS (ESI) *m/z* 509.1 $[M+H]^+$.

Step5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,7-dichloro-1H-indole-2-carboxamide

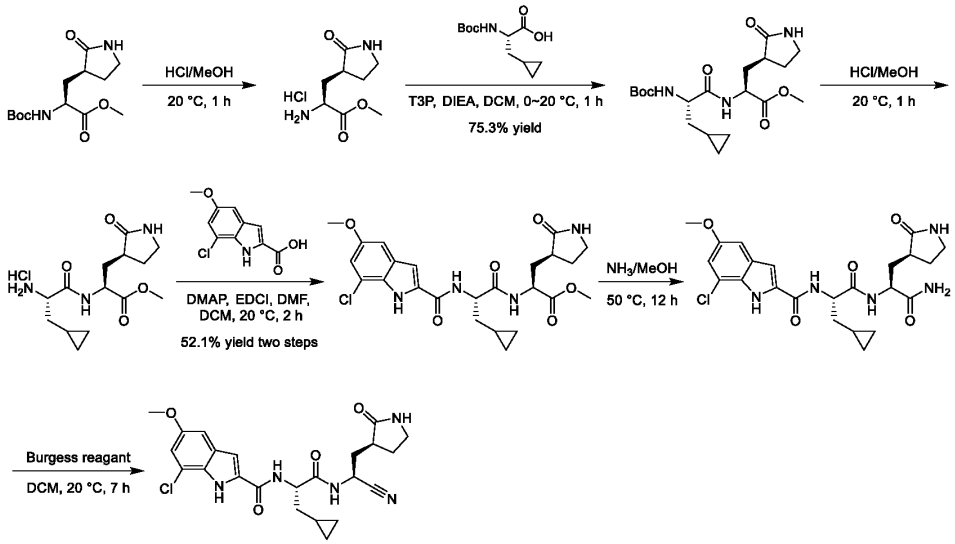
[000709] A mixture of methyl (2*S*)-2-[[(2*S*)-3-cyclopropyl-2-[(4,7-dichloro-1*H*-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (550 mg, 1.08 mmol, 1 *eq*) in NH_3/methanol (7 M, 154.25 uL, 1 *eq*) was stirred at 60 °C for 12 h. Upon completion, the mixture was concentrated under reduced pressure to give *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,7-dichloro-1*H*-indole-2-carboxamide (500 mg, crude) as white solid. MS (ESI) *m/z* 494.1 $[M+H]^+$.

Step6: 4,7-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000710] A mixture of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,7-dichloro-1*H*-indole-2-carboxamide (450 mg, 910.25 umol, 1 *eq*) and Burgess reagent (1.30 g, 5.46 mmol, 6 *eq*) in DCM (10 mL) was stirred at 20 °C for 9 h. Upon completion, the mixture was concentrated under reduced pressure to give the residue. Then the residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80 * 40 mm * 3um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 25% - 55%, 8 min) to give the product 4,7-dichloro-*N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1*H*-indole-2-carboxamide (300 mg, 629.78 umol, 69.19% yield, 100% purity) as a white solid. MS (ESI) *m/z* 476.1 $[M+H]^+$.

[000711] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.66 - 7.56 (m, 1H), 7.52 - 7.45 (m, 1H), 7.22 - 7.14 (m, 1H), 5.16 - 5.05 (m, 1H), 4.68 - 4.61 (m, 1H), 3.36 - 3.32 (m, 2H), 2.70 - 2.57 (m, 1H), 2.40 - 2.27 (m, 2H), 1.99 - 1.69 (m, 4H), 0.91 - 0.79 (m, 1H), 0.62 - 0.52 (m, 2H), 0.27 - 0.15 (m, 2H).

Example 74. Synthesis of viral protease inhibitor compound 695



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[00712] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (2 g, 6.99 mmol, 1 eq) in HCl/EtOAc (4 M, 40.00 mL, 22.91 eq), the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.5 g, crude, HCl) as a white solid.

Step 2: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[00713] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.4 g, 6.29 mmol, 1 eq, HCl) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (1.44 g, 6.29 mmol, 1.00 eq) in DCM (30 mL) at 0 °C was added DIEA (3.25 g, 25.15 mmol, 4.38 mL, 4 eq) and T_3P (12.00 g, 18.86 mmol, 11.22 mL, 50% purity, 3 eq) was added dropwise, and then the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (60 mL) at 0 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 5:1 to 0:1) to give the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-

yl]propanoate (1.9 g, 4.73 mmol, 75.27% yield, 99% purity) as a yellow solid. MS (ESI) *m/z* 398.4 $[M+H]^+$.

Step 3: (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[000714] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.8 g, 2.01 mmol, 1 eq) in HCl/MeOH (4 M, 15 mL, 29.81 eq) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (670 mg, crude, HCl) as a white solid.

Step 4: (S)-methyl 2-((S)-2-(7-chloro-5-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000715] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (670 mg, 2.01 mmol, 1.51 eq, HCl) and 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (300 mg, 1.33 mmol, 1 eq) in DMF (5 mL) was added DMAP (487.32 mg, 3.99 mmol, 3 eq), EDCI (509.78 mg, 2.66 mmol, 2 eq) and DCM (15 mL), and the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (40 mL) at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 5:1 to 0:1) to afford methyl (2S)-2-[[(2S)-2-[(7-chloro-5-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (350 mg, 658.47 umol, 49.52% yield, 95% purity) as a yellow solid. MS (ESI) *m/z* 505.2 $[M+H]^+$.

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-5-methoxy-1H-indole-2-carboxamide

[000716] A solution of methyl(2S)-2-[[(2S)-2-[(7-chloro-5-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (320 mg, 633.71 umol, 1 eq) in NH_3/MeOH (7 M, 40 mL, 441.84 eq) was stirred at 50 °C for 12 h. Upon completion, the reaction mixture was concentrated under

reduced pressure to give the product N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-5-methoxy-1H-indole-2-carboxamide (290 mg, crude) as a yellow solid. MS (ESI) *m/z* 490.2 $[M+H]^+$.

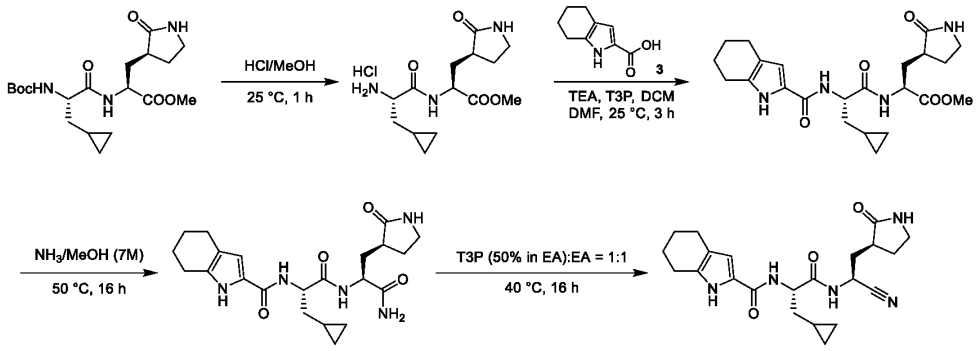
Step 6: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-methoxy-1H-indole-2-carboxamide

[000717] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-5-methoxy-1H-indole-2-carboxamide (270 mg, 551.08 umol, 1 eq) in DCM (10 mL) was added Burgess reagent (393.97 mg, 1.65 mmol, 3 eq). After stirring at 20 °C for 7 h, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 20%-50%,8min) to give the product 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1H-indole-2-carboxamide (139.27 mg, 295.10 umol, 53.55% yield, 100% purity) as a white solid. MS (ESI) *m/z* 472.2 $[M+H]^+$.

[000718] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.17 (s, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 5.08 (dd, *J* = 6.0, 10.3 Hz, 1H), 4.55 (t, *J* = 7.4 Hz, 1H), 3.82 (s, 3H), 3.30 - 3.27 (m, 2H), 2.70 - 2.60 (m, 1H), 2.40 - 2.28 (m, 2H), 1.97 - 1.77 (m, 3H), 1.72 - 1.60 (m, 1H), 0.86 (br s, 1H), 0.55 (d, *J* = 8.0 Hz, 2H), 0.20 (dd, *J* = 4.8, 9.4 Hz, 2H)

[000719] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.59 (br s, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.66 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.17 (s, 1H), 7.13 (d, J = 2.2 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 5.00 (q, J = 7.9 Hz, 1H), 4.60 - 4.45 (m, 1H), 3.78 (s, 3H), 3.18 - 3.05 (m, 2H), 2.40 - 2.34 (m, 1H), 2.21 - 2.06 (m, 2H), 1.86 - 1.64 (m, 3H), 1.50 (ddd, J = 6.1, 7.6, 13.9 Hz, 1H), 0.90 - 0.75 (m, 1H), 0.50 - 0.37 (m, 2H), 0.25 - 0.15 (m, 1H), 0.13 - 0.04 (m, 1H)

Example 75. Synthesis of viral protease inhibitor compound 711



Step 1: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000720] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (900 mg, 1.81 mmol, 80% purity, 1 *eq*) in HCl/MeOH (4 M, 12.00 mL, 26.50 *eq*) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to afford methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (600 mg, crude, HCl) as white oil. MS (ESI) *m/z* 298.1 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-(4,5,6,7-tetrahydro-1H-indole-2-carbonylamino)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[000721] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (600 mg, 1.80 mmol, 1 *eq*, HCl) in DCM (7 mL) and DMF (0.5 mL) was added 4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (415.68 mg, 2.52 mmol, 1.4 *eq*), TEA (1.09 g, 10.78 mmol, 1.50 mL, 6 *eq*) and T3P (1.72 g, 2.70 mmol, 1.60 mL, 50% purity, 1.5 *eq*). After stirring at 25 °C for 3 h, the reaction mixture was diluted with water (10 mL) and extracted with DCM (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) and TLC (SiO_2, DCM:MeOH = 10:1) to get the product methyl (2S)-2-[[(2S)-3-cyclopropyl-2-(4,5,6,7-tetrahydro-1H-indole-2-carbonylamino)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (350 mg, 787.36 umol, 43.80% yield) as yellow oil. MS (ESI) *m/z* 445.3 $[M+H]^+$.

Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide

[000722] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-(4,5,6,7-tetrahydro-1H-indole-2-carbonylamino)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (350 mg, 787.36 umol, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 88.90 *eq*) was stirred at 50 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to afford N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide (300 mg, crude) as yellow solid. MS (ESI) *m/z* 430.2 $[M+H]^+$.

Step 4: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide

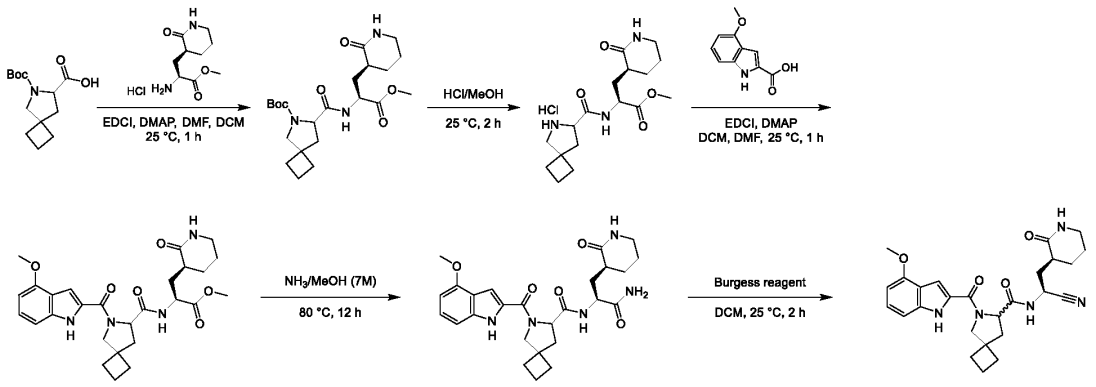
[000723] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide (290 mg, 675.19 umol, 1 *eq*) in T3P (3 mL, 50% purity) and ethyl acetate (3 mL) was stirred at 40 °C for 16 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge BEH C18 100 * 25 mm * 5 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 25% - 55%, 10 min) to afford N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide (61.92 mg, 150.48 umol, 22.29% yield, 100% purity) as white solid. MS (ESI) *m/z* 412.3 $[M+H]^+$.

[000724] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.96 (br s, 1H), 9.00 - 8.77 (m, 1H), 7.89 - 7.66 (m, 2H), 6.60 (br s, 1H), 5.04 - 4.81 (m, 1H), 4.48 - 4.28 (m, 1H), 3.24 - 3.04 (m, 2H), 2.47 - 1.96 (m, 7H), 1.81 - 1.61 (m, 7H), 1.40 (br dd, *J*=6.6, 13.1 Hz, 1H), 0.74 (br s, 1H), 0.38 (br s, 2H), 0.22 - 0.03 (m, 2H).

[000725] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.67 (br s, 1H), 8.74 - 8.49 (m, 1H), 7.53 - 7.28 (m, 2H), 6.54 (d, *J*=2.2 Hz, 1H), 5.05 - 4.84 (m, 1H), 4.54 - 4.38 (m, 1H), 3.17 (br d, *J*=7.2 Hz, 2H), 2.54 (br t, *J*=6.1 Hz, 2H), 2.43 (br t, *J*=5.6 Hz, 3H), 2.28 - 2.08 (m, 2H),

1.90 - 1.79 (m, 1H), 1.77 - 1.65 (m, 6H), 1.56 (qd, *J*=6.7, 13.7 Hz, 1H), 0.83 - 0.70 (m, 1H), 0.42 (br d, *J*=7.8 Hz, 2H), 0.20 - 0.04 (m, 2H).

Example 76. Synthesis of viral protease inhibitor compound 719



Step 1: tert-butyl 7-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate

[000726] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.08 g, 4.57 mmol, 1 *eq*, HCl) and 6-tert-butoxycarbonyl-6-azaspiro[3.4]octane-7-carboxylic acid (1.4 g, 5.48 mmol, 1.2 *eq*) in DCM (15 mL) and DMF (1 mL) was added EDCI (1.75 g, 9.14 mmol, 2 *eq*) and DMAP (1.67 g, 13.71 mmol, 3 *eq*), and the mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 2/1 to 0:1) to give tert-butyl 7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (1.4 g, 2.56 mmol, 56.02% yield, 80% purity) as a yellow oil. MS (ESI) *m/z* 438.3 $[M+H]^+$.

Step 2: tert-butyl 7-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate

[000727] A mixture of tert-butyl 7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (0.7 g, 1.60 mmol, 1 *eq*) in HCl/MeOH (4 M, 20 mL, 50.00 *eq*) was stirred at 25 °C for 2 h. Upon

completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.6 g, crude, HCl) as a white solid. MS (ESI) *m/z* 338.1 $[M+H]^+$.

Step 3: methyl (2S)-2-[[6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000728] To a mixture of methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.6 g, 1.60 mmol, 1 *eq*, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (368.18 mg, 1.93 mmol, 1.2 *eq*) in DCM (10 mL) and DMF (2 mL) was added EDCI (461.47 mg, 2.41 mmol, 1.5 *eq*) and DMAP (588.18 mg, 4.81 mmol, 3 *eq*). After stirring at 25 °C for 1 h, the reaction mixture was diluted with water (50 mL) and extracted with DCM (20 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 2:1 to 0/1) to give methyl (2S)-2-[[6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.65 g, 1.15 mmol, 71.39% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 511.3 $[M+H]^+$.

Step 4: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000729] A mixture of methyl (2S)-2-[[6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.65 g, 1.15 mmol, 90% purity, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 61.10 *eq*) was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (0.6 g, crude) as a yellow solid. MS (ESI) *m/z* 496.3 $[M+H]^+$.

Step 5: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000730] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (0.58 g, 1.17 mmol, 1 *eq*) in DCM (7 mL) was added Burgess reagent (1.39 g, 5.85 mmol, 5 *eq*), and the solution was stirred at 25 °C for 2 h. Upon completion, the

reaction mixture was diluted with water (30 mL) and extracted with DCM (20 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was separated by prep-TLC (SiO_2, ethyl acetate:MeOH = 20:1) to get N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 1 and N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 2.

[000731] N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 1 was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-55%,8min) to give N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 1 (92.10 mg, 192.86 umol, 16.48% yield, 100% purity) as a white solid. MS (ESI) *m/z* 478.3 $[M+H]^+$.

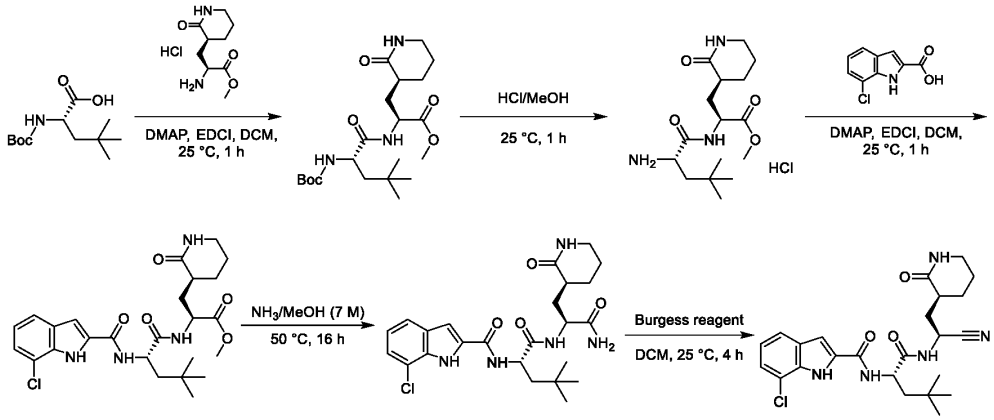
[000732] ^1H NMR (400 MHz, DMSO-d_6) δ = 7.17 - 7.07 (m, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 7.01 - 6.96 (m, 1H), 6.55 - 6.44 (m, 1H), 5.05 - 4.89 (m, 1H), 4.43 (t, *J* = 7.2 Hz, 1H), 4.01 - 3.79 (m, 5H), 3.13 - 2.76 (m, 2H), 2.31 - 2.05 (m, 4H), 2.03 - 1.73 (m, 8H), 1.60 - 0.97 (m, 3H);

[000733] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.49 - 11.19 (m, 1H), 8.81 - 8.41 (m, 1H), 7.31 - 7.20 (m, 1H), 7.11 (br d, *J* = 7.7 Hz, 1H), 7.09 - 7.02 (m, 1H), 7.02 - 6.81 (m, 1H), 6.53 (br d, *J* = 7.7 Hz, 1H), 5.06 - 4.89 (m, 1H), 4.53 (br s, 1H), 4.07 - 3.79 (m, 5H), 3.10 - 3.02 (m, 2H), 2.19 (br s, 4H), 2.06 - 1.31 (m, 11H).

[000734] N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 2 was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-55%,8min) to give N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 2 (30.29 mg, 63.43 umol, 5.42% yield, 100% purity) as a white solid. MS (ESI) *m/z* 478.3 $[M+H]^+$.

[000735] ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 10.26 - 9.64 (m, 1H), 8.99 - 8.34 (m, 1H), 7.26 - 7.16 (m, 1H), 7.15 - 6.74 (m, 2H), 6.62 - 6.32 (m, 1H), 6.27 - 5.80 (m, 1H), 5.06 - 4.83 (m, 1H), 4.81 - 4.54 (m, 1H), 4.14 - 3.82 (m, 5H), 3.31 - 3.03 (m, 2H), 2.56 - 2.35 (m, 2H), 2.35 - 2.16 (m, 2H), 2.11 - 1.73 (m, 9H), 1.52 - 1.23 (m, 2H).

Example 77. Synthesis of viral protease inhibitor compound 721



Step 1: (S)-methyl2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000736] To a solution of (2*S*)-2-(*tert*-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (2.49 g, 10.14 mmol, 1.2 *eq*) and methyl (2*S*)-2-amino-3-[(3*S*)-2-oxo-3-piperidyl] propanoate (2 g, 8.45 mmol, 1 *eq*, HCl) in DCM (60 mL) was added DMAP (3.10 g, 25.35 mmol, 3 *eq*). After EDCI (3.24 g, 16.90 mmol, 2 *eq*) was added, the mixture was stirred at 25 °C for 1 h. Upon the reaction completement, the mixture was quenched by water (400 mL) and was extracted with DCM (150 mL * 3). The organic layer was dried by sat. NaCl (50 mL), concentrated in vacuum and was purified by column (SiO_2, petroleum ether:ethyl acetate = 2:1 to 0:1), washed with HCl (1 M, 150 mL), extracted with DCM (50 mL * 3), and then the pH was adjusted to ~8 with sat. $NaHCO_3$ (30 mL). After extracting with DCM (100 mL), the residue was concentrated in vacuum to obtain (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-4,4- dimethylpentanamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (3 g, 6.32 mmol, 74.74% yield, 90% purity) as a white solid.

[000737] ^{1}H NMR (400MHz, $CDCl_3$-*d*) δ ppm 7.61 (d, *J* = 7.0 Hz, 1H), 6.85 - 6.51 (m, 1H), 6.22 (s, 1H), 5.06 - 4.85 (m, 1H), 4.63 - 4.47 (m, 1H), 4.30 - 4.02 (m, 1H), 3.79 -

3.66 (m, 3H), 3.35 - 3.25 (m, 2H), 2.42 - 2.24 (m, 1H), 2.14 - 2.05 (m, 1H), 1.96 - 1.66 (m, 4H), 1.63 - 1.52 (m, 1H), 1.43 (s, 9H), 1.03 - 0.90 (m, 9H).

Step 2: (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000738] A solution of (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl) amino)-4,4-dimethylpentanamido) -3-((*S*)-2-oxopiperidin-3-yl) propanoate (1.5 g, 3.51 mmol, 1 *eq*) in HCl/MeOH (4 M, 20 mL)n was stirred at 25 °C for 1 h. Upon the reaction completed, the mixture was concentrated in vacuum to obtain (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin -3-yl)propanoate (1.1 g, crude, HCl) as a white solid.

[000739] ^{1}H NMR (400MHz, D_2O) δ ppm 4.57 (dd, *J* = 4.8, 10.3 Hz, 1H), 3.98 (dd, *J* = 5.2, 7.8 Hz, 1H), 3.78 - 3.65 (m, 3H), 3.29 - 3.14 (m, 2H), 2.75 - 2.33 (m, 1H), 2.24 - 1.47 (m, 8H), 1.04 - 0.86 (m, 9H).

Step 3: (S)-methyl2-((S)-2-(7-chloro-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000740] To a solution of (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin -3-yl)propanoate (550 mg * 2, HCl salt, 1.68 mmol, 1 *eq*) and 7-chloro-1*H*-indole-2-carboxylic acid (394.29 mg, 2.02 mmol, 1.2 *eq*) in DCM (6 mL) was added DMAP (615.66 mg, 5.04 mmol, 3 *eq*), and then was added EDCI (644.05 mg, 3.36 mmol, 2 *eq*) to the mixture at 25 °C. After stirring at 25 °C for 1 h, the mixture was quenched by water (200 mL) and was extracted with DCM (70 mL * 3), then was concentrated in vacuum and was purified by column (SiO_2, petroleum ether:ethyl acetate = 1:1 to 0:1) and was concentrated in vacuum, then was washed with 1M HCl (100 mL) and was extracted with DCM (30 mL * 3) and the pH of the organic phase was adjusted to pH~7 with sat. $NaHCO_3$ (30 mL). The residue was concentrated in vacuum to obtain (*S*)-methyl 2-((*S*)-2-(7-chloro-1*H*-indole-2-carboxamido)-4,4-dimethylpentanamido) -3-((*S*)-2-oxopiperidin-3-yl)propanoate (650 mg, 1.16 mmol, 40 % yield, 90% purity) as a light yellow solid. MS (ESI) *m/z* 505.2 $[M+H]^+$

[000741] ^{1}H NMR (400MHz, MeOD-d_4) δ ppm 7.58 (d, J = 7.8 Hz, 1H), 7.32 - 7.17 (m, 2H), 7.06 (t, J = 7.8 Hz, 1H), 4.73 (dd, J = 3.8, 8.6 Hz, 1H), 4.55 (dd, J = 4.0, 11.7 Hz, 1H), 3.71 (s, 3H), 3.35 (s, 1H), 3.24 - 3.01 (m, 2H), 2.49 - 2.22 (m, 2H), 2.02 - 1.40 (m, 8H), 1.08 - 0.96 (m, 9H).

Step 4:

N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-1H-indole-2-carboxamide

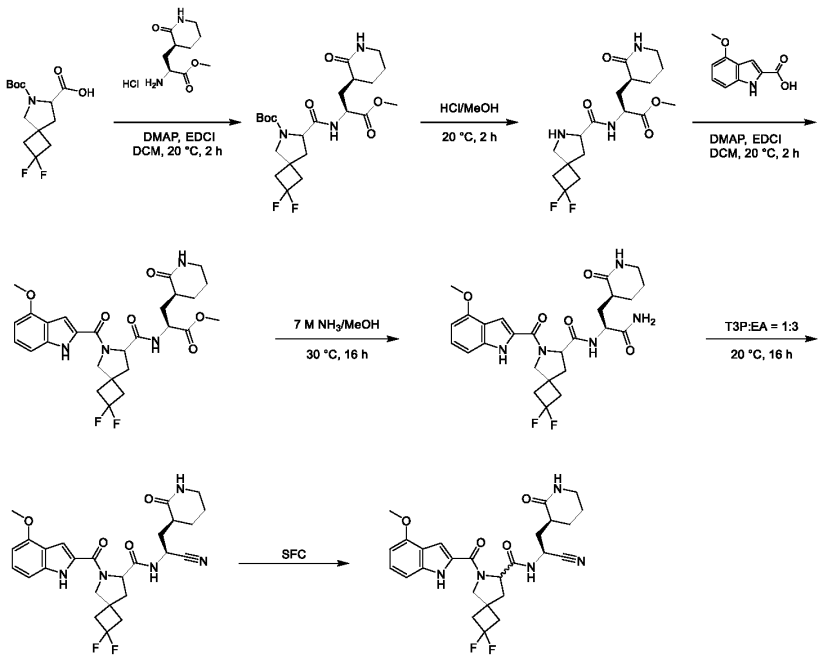
[000742] A solution of (*S*)-methyl 2-((*S*)-2-(7-chloro-1*H*-indole-2-carboxamido)-4,4-dimethylpentanamido) -3-((*S*)-2-oxopiperidin-3-yl)propanoate (650 mg, 1.29 mmol, 1 *eq*) in NH_3/MeOH (7M, 10 mL) was stirred at 50 °C for 16 h. Upon the reaction completement, the mixture was concentrated in vacuum to obtained *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl) amino)-4,4- dimethyl-1-oxopentan-2-yl)-7-chloro-1*H*-indole-2-carboxamide (450 mg, crude) as a light yellow solid. MS (ESI) *m/z* 490.3 $[M+H]^+$.

Step 5: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-1H-indole-2-carboxamide

[000743] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl) amino)-4,4- dimethyl-1-oxopentan-2-yl)-7-chloro-1*H*-indole-2-carboxamide (430 mg, 877.56 umol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (627.38 mg, 2.63 mmol, 3 *eq*), and the reaction was stirred at 25 °C for 4 h. Upon the reaction completement, the mixture was quenched by water (10 mL) and was dried by blowing N_2 and was purified by prep-HPLC (column: Kromasil C18 (250*50mm*10 um); mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 35%-65%, 10min) to obtain 7-chloro-*N*-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-1*H*-indole-2-carboxamide (205 mg, 424.79 umol, 48.41% yield, 97.8% purity) as a white solid. MS (ESI) *m/z* 472.2 $[M+H]^+$.

[000744] ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 11.70 (s, 1H), 9.02 (d, J = 8.0 Hz, 1H), 8.71 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.34 - 7.23 (m, 2H), 7.07 (t, J = 7.8 Hz, 1H), 5.05 (q, J = 8.2 Hz, 1H), 4.63 - 4.54 (m, 1H), 3.07 (s, 2H), 2.30 - 2.18 (m, 2H), 1.88 - 1.32 (m, 7H), 0.95 (s, 9H).

Example 78. Synthesis of viral protease inhibitor compound 723



Step 1: tert-butyl 2,2-difluoro-7-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate

[000745] A mixture of (7S)-6-tert-butoxycarbonyl-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxylic acid (500 mg, 1.72 mmol, 1 *eq*), methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (406.29 mg, 1.72 mmol, 1 *eq*, HCl), EDCI (987.17 mg, 5.15 mmol, 3 *eq*), DMAP (629.10 mg, 5.15 mmol, 3 *eq*) in DCM (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 2 h under N_2 atmosphere. Upon completion, the reaction mixture was poured into H_2O (25 mL) at 20 °C, and then extracted with DCM (25 mL * 3). The combined organic layers were washed with brine (25 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 1/1) to afford tert-butyl (7S)-2,2-difluoro-7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (800 mg, crude) as a white solid. MS (ESI) *m/z* 474.1 $[M+H]^+$.

Step 2: (2S)-methyl 2-(2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000746] A solution of tert-butyl (7S)-2,2-difluoro-7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (710 mg, 1.50 mmol, 1 *eq*) in HCl/MeOH (4 M, 8 mL, 21.34 *eq*) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl (2S)-2-[[(7S)-2,2-difluoro-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (614 mg, crude, HCl) as a yellow oil. MS (ESI) *m/z* 374.1 $[M+H]^+$.

Step 3: (2S)-methyl 2-(2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000747] To a solution of methyl (2S)-2-[[(7S)-2,2-difluoro-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (614 mg, 1.50 mmol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (286.41 mg, 1.50 mmol, 1 *eq*), DMAP (549.06 mg, 4.49 mmol, 3 *eq*) in DCM (7 mL) was added EDCI (861.56 mg, 4.49 mmol, 3 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O (25 mL) at 20 °C, and then extracted with DCM (25 mL * 3). The combined organic layers were washed with brine (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 80/1 to 1/1) to give methyl (2S)-2-[[(7S)-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (550 mg, 1.01 mmol, 67.17% yield) as a yellow solid. MS (ESI) *m/z* 547.2 $[M+H]^+$.

Step 4: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000748] A solution of methyl (2S)-2-[[(7S)-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (535 mg, 978.85 umol, 1 *eq*) in NH_3/MeOH (7 M, 10.70 mL, 76.52 *eq*) was stirred at 30 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to afford (7S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-

azaspiro[3.4]octane-7-carboxamide (520 mg, crude) as a yellow solid. MS (ESI) *m/z* 532.2 $[M+H]^+$.

Step 5: N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000749] A solution of (7S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (515 mg, 968.86 umol, 1 *eq*) in EtOAc (2.5 mL) was added T3P (2.68 g, 4.20 mmol, 2.5 mL, 50% purity, 4.34 *eq*) was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was poured into H_2O (25 mL) at 20 °C, and then extracted with EtOAc (25 mL * 3). The combined organic layers were washed with brine (25 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 45%-75%,10min) to give (7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (188 mg, 364.99 umol, 37.67% yield, 99.7% purity) as a white solid. MS (ESI) *m/z* 514.3 $[M+H]^+$.

Step 6: N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

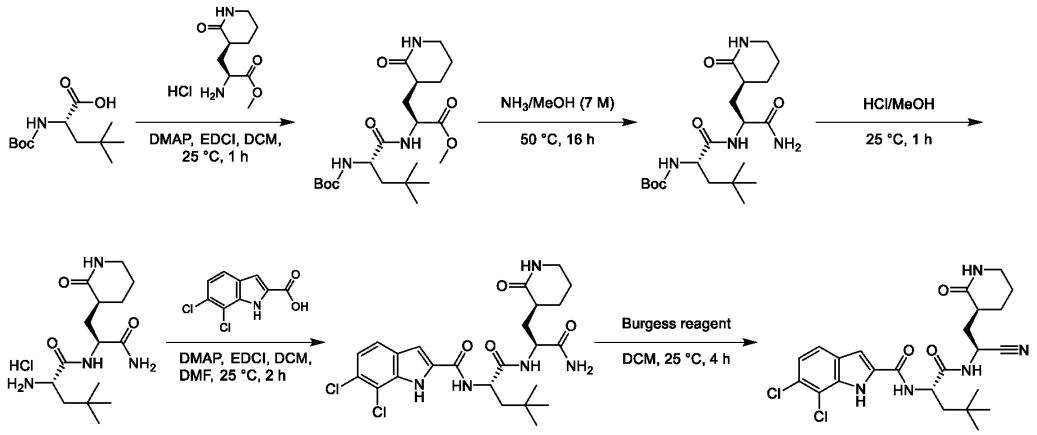
[000750] Isomer 1: (7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (170 mg) was separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 60%-60%,10min) to give (7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (42.5 mg, 82.76 umol, 25.00% yield, 100% purity) as a white solid. MS (ESI) *m/z* 514.3 $[M+H]^+$.

[000751] Isomer 1: ^{1}H NMR (400MHz, MeOD-d_4) δ = 7.26 - 6.72 (m, 3H), 6.53 (d, *J* = 7.6Hz, 1H), 5.03 (d, *J* = 5.7, 10.5Hz, 1H), 4.64 (d, *J* = 1.7Hz, 1H), 4.25 (d, *J* = 10.1Hz, 1H), 4.15 - 4.01 (m, 1H), 3.98 - 3.87 (m, 2H), 4.16 - 3.86 (m, 1H), 3.13 (s, 2H), 2.87 - 2.15 (m, 8H), 1.99 - 1.28 (m, 5H); and to give (7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2,2-difluoro-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-

7-carboxamide (89.8 mg, 173.47 umol, 52.40% yield, 99.2% purity) as a white solid. MS (ESI) *m/z* 514.3 $[M+H]^+$.

[000752] Isomer 2: ^{1}H NMR (400MHz, MeOD-d_4) δ = 7.17 - 6.82 (m, 3H), 6.56 - 6.44 (m, 1H), 5.17 - 5.03 (m, 1H), 4.61 (t, *J* = 7.5Hz, 1H), 4.15 (s, 1H), 4.01 - 3.78 (m, 4H), 3.26 - 2.86 (m, 2H), 2.75 - 2.14 (m, 8H), 2.06 - 1.30 (m, 5H).

Example 79. Synthesis of viral protease inhibitor compound 725



Step 1: (S)-methyl2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000753] To a solution of (2*S*)-2-(*tert*-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (1.24 g, 5.07 mmol, 1.2 *eq*) and methyl (2*S*)-2-amino-3-[(3*S*)-2-oxo-3-piperidyl] propanoate (1 g, 4.22 mmol, 1 *eq*, HCl) in DCM (30 mL) was added DMAP (1.55 g, 12.67 mmol, 3 *eq*), and then was added EDCI (1.62 g, 8.45 mmol, 2 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was quenched by water (400 mL) and was extracted with DCM (150 mL * 3). After drying with sat. NaCl (50 mL), the reaction was concentrated in vacuum. The crude product was purified by column (SiO_2, petroleum ether:ethyl acetate = 2:1 to 0:1) and was washed with 1M HCl (100 mL), extracted with DCM (50 mL * 3), the pH was adjusted to pH~8 with sat. $NaHCO_3$ (50 mL), extracted with DCM (50 mL) and concentrated to afford (*S*)-methyl2-((*S*)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1.4 g, 2.95 mmol, 69.76% yield, 90% purity) as a white solid.

Step 2:tert-butyl((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate

[000754] A solution of (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl) amino)-4, 4-dimethylpentanamido) -3-((*S*)-2-oxopiperidin-3-yl) propanoate (1.4 g, 3.27 mmol, 1 *eq*) in NH_3/MeOH (18 mL, 7M) was stirred at 50 °C for 16 h. Upon completion, the mixture was concentrated in vacuum to give *tert*-butyl((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4- dimethyl-1-oxopentan-2-yl) carbamate (1.1 g, crude) as a white solid.

Step 3: (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide

[000755] A solution of *tert*-butyl ((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl) amino) -4,4-dimethyl-1-oxopentan-2-yl) carbamate (1.5 g, 3.64 mmol, 1 *eq*) in HCl/MeOH (4 M, 20 mL) was stirred at 25 °C for 1 h. Upon the reaction completion, the mixture was concentrated in vacuum to give (*S*)-2-amino-*N*-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)-4,4- dimethylpentanamide (1.2 g, crude) as a white solid.

Step 4: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-6,7-dichloro-1H-indole-2-carboxamide

[000756] A mixture of (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-4,4-dimethyl-pentanamide (900 mg, 2.58 mmol, 1 *eq*, HCl) in DCM (8 mL) and DMF (3 mL) was added DMAP (945.50 mg, 7.74 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added 6,7-dichloro-1H-indole-2-carboxylic acid (593.47 mg, 2.58 mmol, 1 *eq*) and EDCI (1.48 g, 7.74 mmol, 3 *eq*), and the reaction was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5/1 to 0/1) to give N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-6,7-

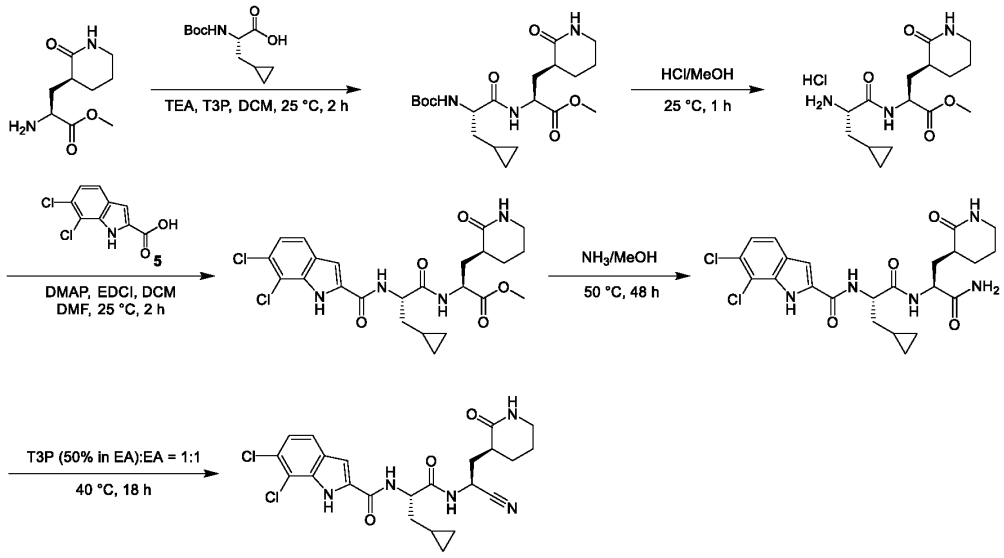
dichloro-1H-indole-2-carboxamide (450 mg, 858.06 umol, 33.26% yield) as a yellow solid. MS (ESI) *m/z* 524.2 $[M+H]^+$.

Step 5: 6,7-dichloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1H-indole-2-carboxamide

[000757] To a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-6,7-dichloro-1H-indole-2-carboxamide (400 mg, 762.72 umol, 1 eq) in DCM (5 mL) was added Burgess reagent (363.53 mg, 1.53 mmol, 2 eq) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was quenched by addition H_2O (3 mL), and then combined organic layer was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH3H2O+10mM NH4HCO3)-ACN];B%: 35%-65%,8min) to give 6,7-dichloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1H-indole-2-carboxamide (165 mg, 325.81 umol, 42.72% yield) as a white solid. MS (ESI) *m/z* 506.1 $[M+H]^+$.

[000758] ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.54 (d, *J*=8.4 Hz, 1H), 7.25 - 7.16 (m, 2H), 5.13 - 5.05 (m, 1H), 4.66 (dd, *J*=4.3, 8.3 Hz, 1H), 3.25 - 3.13 (m, 2H), 2.50 - 2.35 (m, 2H), 1.99 - 1.88 (m, 2H), 1.87 (d, *J*=4.4 Hz, 1H), 1.79 (br dd, *J*=8.4, 14.6 Hz, 2H), 1.71 - 1.56 (m, 1H), 1.55 - 1.43 (m, 1H), 1.03 (s, 9H).

Example 80. Synthesis of viral protease inhibitor compound 727



Step 1: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000759] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.3 g, 5.49 mmol, 1 *eq*, HCl) in DCM (12 mL) was added (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (1.51 g, 6.59 mmol, 1.2 *eq*), TEA (3.33 g, 32.95 mmol, 4.59 mL, 6 *eq*) and T3P (5.24 g, 8.24 mmol, 4.90 mL, 50% purity, 1.5 *eq*). The reaction was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, DCM:MeOH = 10:1) and TLC (SiO_2, DCM:MeOH = 10:1) to afford methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.99 g, 4.11 mmol, 74.84% yield, 85% purity) as a yellow oil. MS (ESI) *m/z* 412.2 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000760] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.20 g, 2.48 mmol, 85% purity, 1 *eq*) in HCl/MeOH (4 M, 15 mL, 24.21 *eq*) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then

was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to afford methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (850 mg, crude, HCl) as a yellow oil. MS (ESI) *m/z* 312.1 $[M+H]^+$.

Step 3: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(6,7-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000761] A mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (850 mg, 2.44 mmol, 1 *eq*, HCl) in DCM (10 mL) and DMF (0.5 mL) was added with 6,7-dichloro-1H-indole-2-carboxylic acid (674.59 mg, 2.93 mmol, 1.2 *eq*, 1.2), DMAP (746.35 mg, 6.11 mmol, 2.5 *eq*) and EDCI (936.91 mg, 4.89 mmol, 2 *eq*), and then the resulting mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, DCM:MeOH = 10:1) and TLC (SiO_2, DCM:MeOH = 10:1) to afford methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(6,7-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.24 g, 1.50 mmol, 61.27% yield, 63% purity) as a yellow solid. MS (ESI) *m/z* 523.2 $[M+H]^+$.

Step 4: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6,7-dichloro-1H-indole-2-carboxamide

[000762] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(6,7-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.38 g, *3* batches in parallel, 726.01 umol, 1 *eq*) in NH_3/MEOH (7 M, 12.06 mL, 116.31 *eq*) was stirred at 50 °C for 48 h. Upon completion, The mixture was concentrated under reduced pressure to give a residue, and then was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to afford N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6,7-dichloro-1H-indole-2-carboxamide (1 g, crude) as a yellow oil. MS (ESI) *m/z* 508.2 $[M+H]^+$.

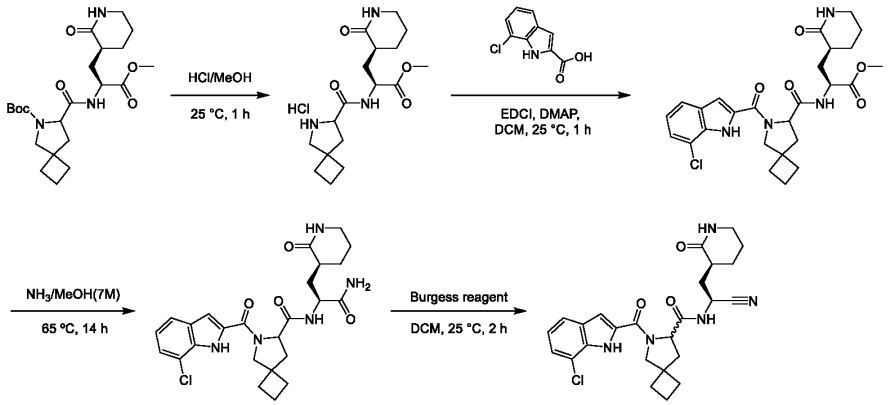
Step 5: 6,7-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000763] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6,7-dichloro-1H-

indole-2-carboxamide (1 g, 1.97 mmol, 1 *eq*) in T3P (5 mL, 50% purity) and ethyl acetate (5 mL) was stirred at 40 °C for 18 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (20 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 8 min) to get the product 6,7-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (288.22 mg, 587.75 umol, 29.88% yield, 100% purity) as a white solid. MS (ESI) *m/z* 490.1 $[M+H]^+$.

[000764] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.94 (br s, 1H), 9.01 (d, *J*=7.9 Hz, 1H), 8.76 (br d, *J*=7.5 Hz, 1H), 7.66 (d, *J*=8.4 Hz, 1H), 7.55 (br s, 1H), 7.33 - 7.21 (m, 2H), 5.21 - 4.90 (m, 1H), 4.60 - 4.38 (m, 1H), 3.16 - 3.01 (m, 2H), 2.35 - 2.18 (m, 2H), 1.90 - 1.65 (m, 4H), 1.63 - 1.33 (m, 3H), 0.80 (br d, *J*=5.5 Hz, 1H), 0.49 - 0.35 (m, 2H), 0.26 - 0.05 (m, 2H).

Example 81. Synthesis of viral protease inhibitor compound 729



Step 1: (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(6-azaspiro[3.4]octane-7-carboxamido)propanoate

[000765] A solution of tert-butyl 7-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate (1 g, 2.29 mmol, 1 eq) in HCl/MeOH (40 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove HCl/MeOH, and then DCM (50 mL)

(three times) was added. The reaction was concentrated under reduced pressure to give a crude product (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(6-azaspiro[3.4]octane-7-carboxamido)propanoate (800 mg, crude, HCl) was obtained as a yellow solid. MS (ESI) m/z 338.2 $[M+H]^+$.

Step 2: (2S)-methyl 2-(6-(7-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000766] To a solution of (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(6-azaspiro[3.4]octane-7-carboxamido)propanoate (580 mg, 1.72 mmol, 1 *eq*) and 7-chloro-1H-indole-2-carboxylic acid (504.35 mg, 2.58 mmol, 1.5 *eq*) in DCM (10 mL) was added DMAP (420.00 mg, 3.44 mmol, 2 *eq*) and EDCI (494.29 mg, 2.58 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction was quenched by H_2O (100 mL) and then extracted with DCM (50 mL * 3). The combined organic phase was washed with brine (50 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1 to 0/1) to afford (2S)-methyl 2-(6-(7-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (680 mg, 1.19 mmol, 69.13% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 515.2 $[M+H]^+$.

Step 3: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(7-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000767] To a solution of methyl (2S)-2-[[6-(7-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (675 mg, 1.31 mmol, 1 *eq*) in NH_3 (7 M, in MeOH, 29.53 mL, 157.72 *eq*). The mixture was stirred at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The mixture was added with DCM (50 mL) (three times), and then the reaction was concentrated under reduced pressure to give a residue. The crude product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(7-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (700 mg, crude) was used into the next step and obtained as a yellow solid. MS (ESI) *m/z* 500.2 $[M+H]^+$.

Step 4: 6-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide

[000768] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(7-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (695 mg, 1.39 mmol, 1 *eq*) in DCM (15 mL) was added Burgess reagent (1.66 g, 6.95 mmol, 5 *eq*) under N_2. The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue at 30 °C. The residue was purified by prep-TLC (SiO_2, ethyl acetate:MeOH = 20:1) to give desired compound (450 mg, purity 96%) as a yellow solid, which was further separated by SFC (condition:column: DAICEL CHIRALPAK AS(250mm * 30mm, 10um); mobile phase: [Neu-ETOH];B%: 50%-50%,min) to give 6-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide (145 mg, 300.85 umol, 21.64% yield, 100% purity) as a white solid. MS (ESI) *m/z* 482.3 $[M+H]^+$.

[000769] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.67 - 7.49 (m, 1H), 7.31 - 7.23 (m, 1H), 7.19 - 6.99 (m, 2H), 5.14 - 4.95 (m, 1H), 4.60 - 4.52 (m, 1H), 4.07 - 3.77 (m, 2H), 3.27 - 3.16 (m, 2H), 2.56 - 1.50 (m, 15H).

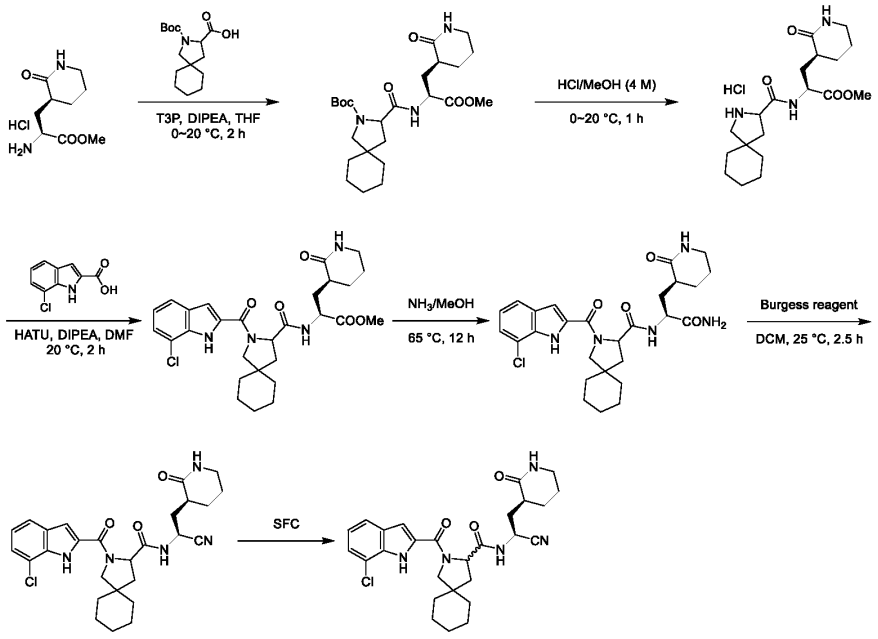
[000770] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.27 - 11.09 (m, 1H), 8.82 - 8.62 (m, 1H), 7.72 - 7.53 (m, 1H), 7.36 - 7.24 (m, 2H), 7.19 - 7.02 (m, 2H), 5.11 - 4.85 (m, 1H), 4.67 - 4.42 (m, 1H), 4.05 - 3.73 (m, 2H), 3.10 - 3.06 (m, 2H), 2.30 - 1.38 (m, 15H).

[000771] 6-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide (170 mg, 348.13 umol, 25.04% yield, 98.7% purity) as a white solid. MS (ESI) *m/z* 482.3 $[M+H]^+$.

[000772] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.67 - 7.55 (m, 1H), 7.31 - 7.25 (m, 1H), 7.18 - 7.11 (m, 1H), 7.10 - 7.04 (m, 1H), 4.93 (br s, 1H), 4.60 - 4.54 (m, 1H), 4.13 - 3.79 (m, 2H), 2.98 (br s, 2H), 2.42 - 1.54 (m, 15H).

[000773] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.27 - 10.98 (m, 1H), 8.88 - 8.54 (m, 1H), 7.82 - 7.49 (m, 1H), 7.34 - 6.98 (m, 4H), 5.10 - 4.95 (m, 1H), 4.69 - 4.39 (m, 1H), 4.03 - 3.72 (m, 2H), 3.10 - 3.05 (m, 2H), 2.32 - 1.39 (m, 15H).

Example 82. Synthesis of viral protease inhibitor compound 731



Step 1: tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate

[000774] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 4.22 mmol, 1 *eq*, HCl) and 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (1.26 g, 4.44 mmol, 1.05 *eq*), DIPEA (2.73 g, 21.12 mmol, 3.68 mL, 5 *eq*) in THF (10 mL) was added T3P (4.03 g, 6.34 mmol, 3.77 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 20 °C for 2 h. Upon completion, the residue was poured into saturated sodium bicarbonate solution (30 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (20 mL * 2). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5/1 to 0/1) to afford tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1- [[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (1.6 g, crude) as alight yellow oil. MS (ESI) *m/z* 466.3 $[M+H]^+$.

Step 2: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000775] To a mixture of tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl] ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (1.6 g, 3.44 mmol, 1 *eq*) was added HCl/MeOH (4 M, 16.00 mL, 18.62 *eq*) at 0 °C under N_2. The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated to get methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.5 g, crude, HCl) as a light yellow oil. MS (ESI) *m/z* 366.2 $[M+H]^+$.

Step 3: methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000776] To a mixture of methyl(2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3- piperidyl]propanoate (1.5 g, 3.73 mmol, 1 *eq*, HCl) and 7-chloro-1H-indole-2-carboxylic acid (729.99 mg, 3.73 mmol, 1 *eq*), DIPEA (1.45 g, 11.20 mmol, 1.95 mL, 3 *eq*) in DMF (10 mL) was added HATU (1.70 g, 4.48 mmol, 1.2 *eq*) at 20 °C under N_2. The mixture was stirred at 20 °C for 2 h. Upon completion, the residue was poured into ice-water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (5 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 2/1 to 0/1) to afford methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.60 g, crude) as a light yellow oil. MS (ESI) *m/z* 543.2 $[M+H]^+$.

Step 4: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000777] To a mixture of methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane -3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.6 g, 2.95 mmol, 1 *eq*) was added NH_3/MeOH (7 M, 22.86 mL, 54.31 *eq*) at 20 °C under N_2. The mixture was stirred at 65 °C for 12 h. Upon completion, the mixture was cooled to 25 °C and concentrated in reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5/1 to 0/1) to give N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-1H-indole -2-

carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.2 g, crude) as a light yellow solid. MS (ESI) *m/z* 528.2 $[M+H]^+$.

Step 5: 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[000778] To a mixture of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2- (7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.2 g, 2.27 mmol, 1 *eq*) in DCM (5 mL) was added Burgess reagent (1.2 g, 5.04 mmol, 2.22 *eq*) in one portion at 20 °C under N_2. The mixture was stirred at 20 °C for 2.5 h. Upon completion, the mixture was added water (3 mL) and stirred for 20 min, then concentrated to get the crude. The residue was purified by prep-TLC (SiO_2, EtOAc:MeOH = 25:1) to afford 2-(7-chloro-1H-indole-2-carbonyl) -N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (0.75 g, 1.45 mmol, 64.00% yield, 98.9% purity) as a light yellow solid. MS (ESI) *m/z* 528.2 $[M+H]^+$.

Step 6: 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[000779] 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (0.9 g, 1.76 mmol, 1 *eq*) was separated by chiral separation (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 60%-60%,6.7min) to afford 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (298.31 mg, 578.46 umol, 32.78% yield, 98.9% purity) as a white solid. MS (ESI) *m/z* 510.3 $[M+H]^+$.

[000780] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.62 (br d, *J* = 7.94 Hz, 1 H), 7.56 - 7.56 (m, 1 H), 7.22 - 7.30 (m, 1 H), 7.01 - 7.13 (m, 2 H), 5.11 (br dd, *J* = 10.58, 5.73 Hz, 1 H), 4.62 (br dd, *J* = 9.81, 7.83 Hz, 1 H), 3.83 - 3.96 (m, 1 H), 3.71 (br d, *J* = 10.36 Hz, 1 H), 3.16 - 3.27 (m, 2 H), 2.40 - 2.62 (m, 2 H), 1.70 - 2.08 (m, 4 H), 1.29 - 1.65 (m, 12 H).

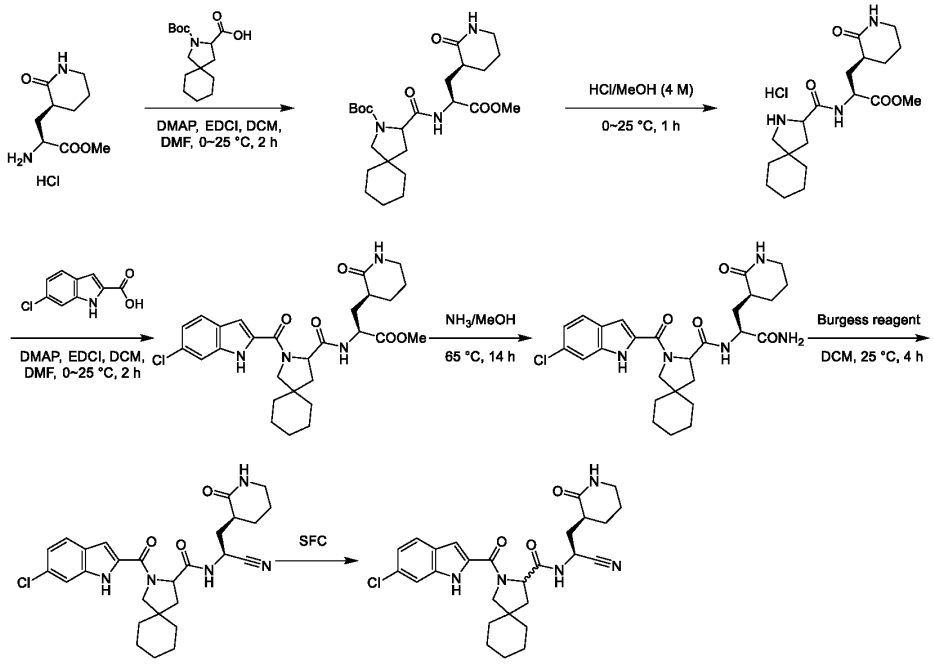
[000781] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.15 (br s, 1 H), 8.71 (br s, 1 H), 7.62 (br s, 1 H), 7.18 - 7.35 (m, 2 H), 6.94 - 7.13 (m, 2 H), 4.96 (br s, 1 H), 4.62 (br s, 1 H), 3.51 - 3.87 (m, 2 H), 3.09 - 3.20 (m, 2 H), 2.09 - 2.36 (m, 3 H), 1.60 - 1.89 (m, 4 H), 1.19 - 1.55 (m, 12 H).

[000782] To give 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl] -2-azaspiro[4.5]decane-3-carboxamide Isomer 2 (252.99 mg, 487.10 umol, 27.60% yield, 98.20% purity) as the white solid. MS (ESI) *m/z* 510.3 $[M+H]^+$;

[000783] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.64 (d, J=7.72 Hz, 1 H), 7.21 - 7.33 (m, 1 H), 7.12 (s, 1 H), 7.04 - 7.10 (m, 1 H), 7.07 (t, J=7.83 Hz, 1 H), 5.02 (dd, J=10.25, 6.06 Hz, 1 H), 4.62 (dd, J=9.70, 7.72 Hz, 1 H), 3.95 (br d, J=10.14 Hz, 1 H), 3.77 (br d, J=10.58 Hz, 1 H), 3.01 - 3.22 (m, 2 H), 2.22 - 2.40 (m, 3 H), 1.86 - 2.04 (m, 2 H), 1.77 - 1.86 (m, 1 H), 1.72 (br dd, J=12.46, 10.03 Hz, 1 H), 1.39 - 1.68 (m, 12 H).

[000784] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.10 (br s, 1 H), 8.65 (br d, J = 6.24 Hz, 1 H), 7.63 (br d, J = 6.85 Hz, 1 H), 7.17 - 7.34 (m, 2 H), 7.08 (br t, J = 7.70 Hz, 2 H), 4.99 (br d, J = 7.46 Hz, 1 H), 4.61 (br s, 1 H), 3.56 - 3.89 (m, 2 H), 3.10 (br s, 2 H), 2.09 - 2.31 (m, 3 H), 1.64 - 1.95 (m, 4 H), 1.38 - 1.62 (m, 12 H).

Example 83. Synthesis of viral protease inhibitor compound 733



Step 1: tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate

[000785] To a solution of methyl (S)-methyl 2-amino-3-((S)-2-oxopiperidin-3-yl)propanoate (500 mg, 2.11 mmol, 1 *eq*, HCl) in DCM (4 mL) and DMF (2 mL) was added 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (718.30 mg, 2.53 mmol, 1.2 *eq*), DMAP (774.22 mg, 6.34 mmol, 3 *eq*), and then EDCI (809.90 mg, 4.22 mmol, 2 *eq*) at 0 °C. The mixture was then stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 1:0 to 10:1) to give tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate (775 mg, 1.50 mmol, 70.92% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 466.3 $[M+H]^+$.

Step 2: (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate

[000786] A mixture of *tert*-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate (775 mg, 1.50 mmol, 90% purity, 1 *eq*) in HCl/MeOH (4 M, 8 mL, 21.36 *eq*) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate (800 mg, crude, HCl) as a yellow solid.

Step 3: (2S)-methyl 2-(2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000787] To a solution of (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate (740 mg, 1.38 mmol, 75% purity, 1 *eq*, HCl) in DCM (6 mL) and DMF (3 mL) was added 6-chloro-1H-indole-2-carboxylic acid (297.11 mg, 1.52 mmol, 1.1 *eq*), DMAP (506.09 mg, 4.14 mmol, 3 *eq*), then EDCI (529.42 mg, 2.76 mmol, 2 *eq*) at 0 °C, and then the mixture was then stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 1:0 to 10:1)

to give (2S)-methyl 2-(2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (980 mg, 1.35 mmol, 98.02% yield, 75% purity) as a yellow solid. MS (ESI) *m/z* 543.3 $[M+H]^+$.

Step 4: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000788] A mixture of (2S)-methyl 2-(2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (980 mg, 1.35 mmol, 75% purity, 1 *eq*) in NH_3.MeOH (7 M, 15 mL, 77.58 *eq*) was stirred at 65 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (960 mg, crude) as a yellow solid. MS (ESI) *m/z* 528.2 $[M+H]^+$.

Step 5: 2-(6-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[000789] To a solution of N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (960 mg, 1.36 mmol, 75% purity, 1 *eq*) in DCM (10 mL) was added Burgess reagent (1.95 g, 8.18 mmol, 6 *eq*) and then stirred at 25 °C for 4 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250*50mm*10 um); mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 35%-65%, 10min) to give 2-(6-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (280 mg, 39.66% yield, 98.5% purity) as a white solid. MS (ESI) *m/z* 510.2 $[M+H]^+$.

Step 6: 2-(6-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[000790] 2-(6-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (280 mg, 98.5% purity) was purified by SFC (column: REGIS(S, S)WHELK-O1 (250 mm*25 mm,10 um); mobile phase: [0.1% NH_3H_2O IPA]; B%: 60% - 60%, 8min) to give 2-(6-chloro-1H-indole-2-carbonyl)-N-

((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (90.34 mg, 175.89 umol, 12.90% yield, 99.3% purity) as a white solid. MS (ESI) *m/z* 510.2 $[M+H]^+$.

[000791] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.68 (s, 1H), 9.10 - 8.79 (m, 1H), 7.69 (d, *J*=8.4 Hz, 1H), 7.58 - 7.47 (m, 1H), 7.46 - 7.36 (m, 1H), 7.14 - 6.62 (m, 2H), 5.10 - 4.73 (m, 1H), 4.51 (t, *J*=8.4 Hz, 1H), 3.95 - 3.73 (m, 1H), 3.65 (d, *J*=10.4 Hz, 1H), 3.17 - 2.83 (m, 2H), 2.35 - 2.07 (m, 3H), 1.93 - 1.19 (m, 16H).

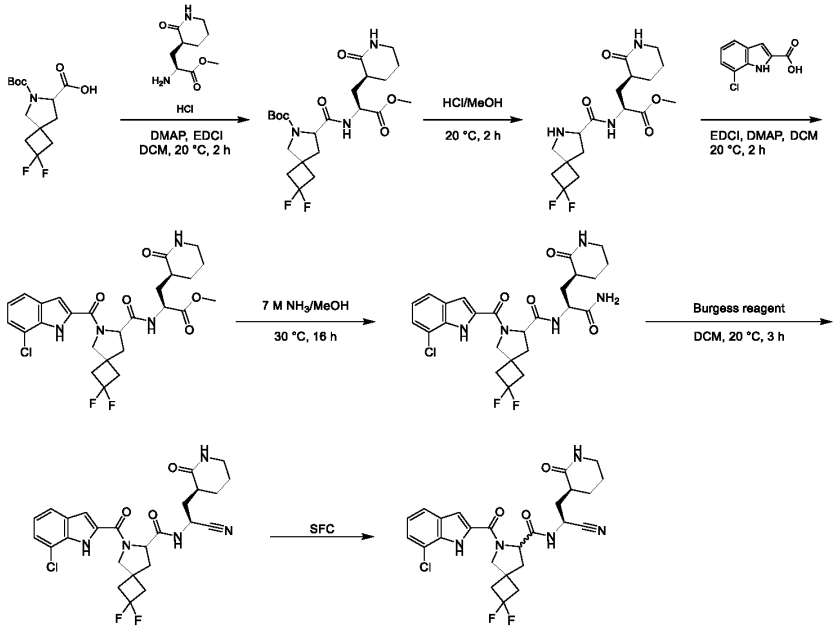
[000792] ^{1}H NMR (400MHz, DMSO-d_6)(T=273+80K) δ = 11.48 (br s, 1H), 8.74 (br s, 1H), 7.65 (br s, 1H), 7.47 (br s, 1H), 7.31 (br s, 1H), 7.06 (br d, *J*=9.0 Hz, 2H), 4.98 (br s, 1H), 4.57 (br s, 1H), 3.87 (br d, *J*=10.1 Hz, 1H), 3.64 (br s, 1H), 3.10 - 3.04 (m, 2H), 2.39 - 2.11 (m, 3H), 1.90 - 1.36 (m, 16H).

[000793] To give 2-(6-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 2 (143.12 mg, 280.61 umol, 20.58% yield, 100% purity) as a white solid. MS (ESI) *m/z* 510.2 $[M+H]^+$.

[000794] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.69 (s, 1H), 9.12 - 8.72 (m, 1H), 7.69 (d, *J*=8.6 Hz, 1H), 7.57 - 7.40 (m, 2H), 7.14 - 6.60 (m, 2H), 5.08 - 4.78 (m, 1H), 4.51 (t, *J*=8.4 Hz, 1H), 3.92 - 3.78 (m, 1H), 3.69 (d, *J*=10.4 Hz, 1H), 3.13 - 2.92 (m, 2H), 2.28 - 2.06 (m, 3H), 1.87 - 1.29 (m, 16H).

[000795] ^{1}H NMR (400MHz, DMSO-d_6) (T=273+80K) δ = 11.49 (br s, 1H), 8.69 (br s, 1H), 7.79 - 7.57 (m, 1H), 7.48 (s, 1H), 7.27 (br s, 1H), 7.06 (br d, *J*=8.4 Hz, 2H), 4.97 (br s, 1H), 4.57 (br s, 1H), 3.88 (d, *J*=10.4 Hz, 1H), 3.68 (br s, 1H), 3.10 - 3.04 (m, 2H), 2.20 (br s, 3H), 1.91 - 1.31 (m, 16H).

Example 83a. Synthesis of viral protease inhibitor compound 743



Step 1: tert-butyl 2,2-difluoro-7-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate

[000796] A mixture of (7S)-6-tert-butoxycarbonyl-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxylic acid (500 mg, 1.72 mmol, 1 *eq*), methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (406.29 mg, 1.72 mmol, 1 *eq*, HCl), EDCI (987.17 mg, 5.15 mmol, 3 *eq*), DMAP (629.10 mg, 5.15 mmol, 3 *eq*) in DCM (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 2 h under N_2 atmosphere. Upon completion, the reaction mixture was poured into H_2O (50 mL) at 20 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 1/1) to give tert-butyl (7S)-2,2-difluoro-7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (800 mg, crude) was obtained as a white solid. MS (ESI) *m/z* 474.1 $[M+H]^+$.

Step 2: (2S)-methyl 2-(2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000797] A solution of tert-butyl (7S)-2,2-difluoro-7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (800 mg, 1.69 mmol, 1 *eq*) in HCl/MeOH (4 M, 8 mL, 18.94 *eq*) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl (2S)-2-[[(7S)-2,2-difluoro-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (690 mg, crude, HCl) as a yellow oil. MS (ESI) *m/z* 374.1 $[M+H]^+$.

Step 3: (2S)-methyl 2-(6-(7-chloro-1H-indole-2-carbonyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000798] To a solution of methyl (2S)-2-[[(7S)-2,2-difluoro-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (690 mg, 1.68 mmol, 1 *eq*, HCl), 7-chloro-1H-indole-2-carboxylic acid (329.30 mg, 1.68 mmol, 1 *eq*), DMAP (617.03 mg, 5.05 mmol, 3 *eq*) in DCM (10 mL), was added EDCI (968.19 mg, 5.05 mmol, 3 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O (35 mL) at 20 °C, and then extracted with (35 mL * 3). The combined organic layers were washed with brine (35 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 80/1 to 1/1) to give methyl (2S)-2-[[(7S)-6-(7-chloro-1H-indole-2-carbonyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (640 mg, 1.16 mmol, 69.00% yield) as a yellow solid. MS (ESI) *m/z* 551.2 $[M+H]^+$.

Step 4: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-6-(7-chloro-1H-indole-2-carbonyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide

[000799] To a solution of methyl (2S)-2-[[(7S)-6-(7-chloro-1H-indole-2-carbonyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (625 mg, 1.13 mmol, 1 *eq*) in NH_3/MeOH (7 M, 12 mL, 74.05 *eq*). The mixture was stirred at 30 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give (7S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(7-chloro-1H-indole-2-carbonyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide (605 mg, crude) as a yellow solid. MS (ESI) *m/z* 536.2 $[M+H]^+$.

Step 5: 6-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide

[000800] To a solution of (7S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(7-chloro-1H-indole-2-carbonyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide (585 mg, 1.09 mmol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (1.17 g, 4.91 mmol, 4.5 *eq*). The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was poured into H_2O (30 mL) at 20 °C, and then extracted with DCM (35 mL *3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min) to give (7S)-6-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide (135 mg, 260.64 umol, 23.88% yield) as a white solid. MS (ESI) *m/z* 518.2 $[M+H]^+$.

Step 6: 6-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide

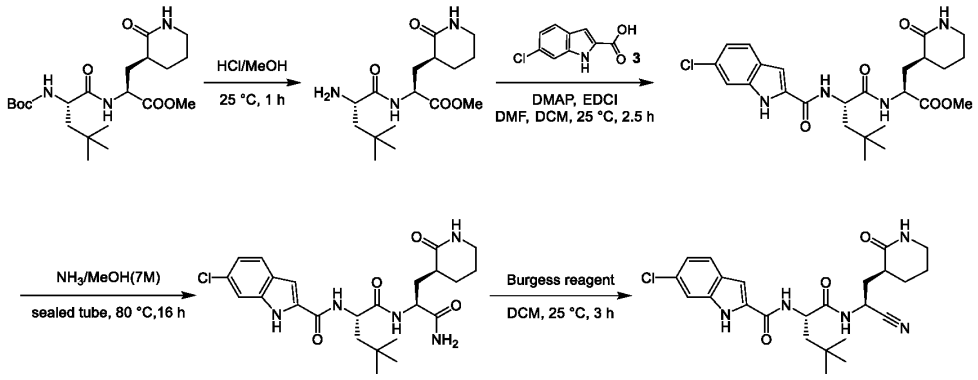
[000801] Isomer 1: 6-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide (133 mg) was separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 60%-60%,15min) to give (7S)-6-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide (48.2 mg, 93.06 umol, 36.24% yield) as a white solid. MS (ESI) *m/z* 518.2 $[M+H]^+$.

[000802] Isomer 1: ^1H NMR (400MHz, DMSO-d_6) δ = 11.34 - 11.12 (m, 1H), 8.83 - 8.63 (m, 1H), 7.71 - 7.55 (m, 1H), 7.30 (d, *J* = 7.1Hz, 2H), 7.13 - 7.04 (m, 1H), 5.09 - 4.92 (m, 1H), 4.71 - 4.52 (m, 1H), 4.20 - 3.87 (m, 2H), 3.09 - 3.05 (m, 1H), 3.10 - 3.03 (m, 2H), 2.91 - 2.52 (m, 4H), 2.48 - 2.35 (m, 2H), 2.29 - 2.08 (m, 2H), 1.96 - 1.31 (m, 5H).

[000803] Isomer 2: To give (7S)-6-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2,2-difluoro-6-azaspiro[3.4]octane-7-carboxamide (83.2 mg, 160.63 umol, 62.56% yield) as a white solid. MS (ESI) *m/z* 518.2 $[M+H]^+$.

[000804] Isomer 2: ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.32 - 11.13 (m, 1H), 8.90 - 8.67 (m, 1H), 7.69 - 7.48 (m, 1H), 7.33 - 7.26 (m, 1H), 7.19 - 6.89 (m, 2H), 5.07 - 4.88 (m, 1H), 4.74 - 4.51 (m, 1H), 4.15 - 3.84 (m, 2H), 3.11 - 3.06 (m, 2H), 3.10 - 3.06 (m, 1H), 2.82 - 2.55 (m, 4H), 2.43 (d, *J* = 3.2, 5.2Hz, 2H), 2.32 - 2.07 (m, 2H), 2.02 - 1.01 (m, 5H).

Example 84. Synthesis of viral protease inhibitor compound 745



Step 1: methyl(2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000805] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 2.34 mmol, 1 *eq*) in HCl/MeOH (4 M) (10 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. Compound methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl -pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (900 mg, crude) was obtained as a white solid and used to the next step directly. MS (ESI) *m/z* 328.3 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-2-[(6-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000806] To a mixture of 6-chloro-1H-indole-2-carboxylic acid (400 mg, 2.04 mmol, 1 *eq*) in DCM (10 mL) and DMF (5 mL) was added DMAP (749.49 mg, 6.13 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added with methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (892.94 mg, 2.45 mmol, 1.20 *eq*, HCl) and EDCI (784.05 mg, 4.09 mmol, 2 *eq*) in one portion at 25 °C and the reaction was stirred for 2.5 h. Upon completion, the reaction mixture was

concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1). Compound methyl (2S)-2-[[(2S)-2-[(6-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (800 mg, 1.58 mmol, 77.47% yield) was obtained as a yellow solid. MS (ESI) *m/z* 505.2 $[M+H]^+$.

Step 3: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-6-chloro-1H-indole-2-carboxamide

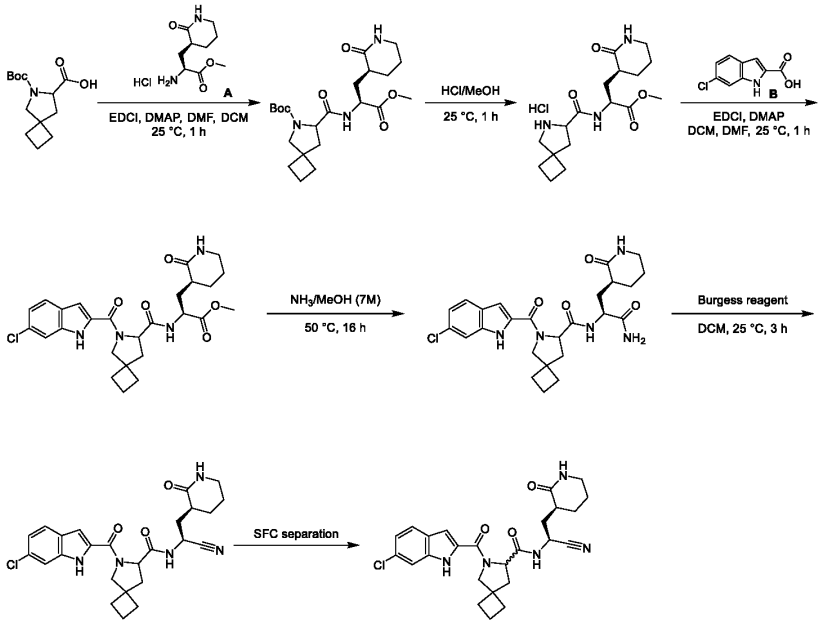
[000807] To a mixture of methyl (2S)-2-[[(2S)-2-[(6-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (605 mg, 1.20 mmol, 1 *eq*) in NH_3/MeOH (7 M) (30.60 mg, 1.80 mmol, 30.00 uL, 1.5 *eq*) in one portion at 25 °C. The mixture was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. Compound N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-6-chloro-1H-indole-2-carboxamide (600 mg, crude) was obtained as a white solid and used to the next step directly. MS (ESI) *m/z* 490.1 $[M+H]^+$.

Step 4: 6-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1H-indole-2-carboxamide

[000808] A mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-6-chloro-1H-indole-2-carboxamide (500 mg, 1.02 mmol, 1 eq) in DCM (6 mL) was added Burgess reagent (607.94 mg, 2.55 mmol, 2.5 eq), and the mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC {column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 40%-60%, 8min}. Compound 6-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1H-indole-2-carboxamide (202 mg, 405.64 umol, 39.75% yield, 94.78% purity) was obtained as a white solid. MS (ESI) *m/z* 472.3 $[M+H]^+$.

[000809] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.41 - 7.65 (m, 2 H), 7.01 - 7.22 (m, 2 H), 5.08 (br s, 1 H), 4.65 (br s, 1 H), 3.15 - 3.25 (m, 2 H), 2.43 (br s, 1 H), 1.46 - 2.05 (m, 8 H), 1.02 (br s, 9 H)

Example 85. Synthesis of viral protease inhibitor compound 791



Step 1: tert-butyl 7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate

[000810] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (2.32 g, 9.79 mmol, 1 *eq*, HCl) in DCM (30 mL) and DMF (10 mL) was added DMAP (3.59 g, 29.38 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added 6-tert-butoxycarbonyl-6-azaspiro[3.4]octane-7-carboxylic acid (3 g, 11.75 mmol, 1.2 *eq*) and EDCI (3.75 g, 19.58 mmol, 2 *eq*) stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (50 mL * 3). The combined organic layers were washed with brine (80 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=5/1 to 0/1) to give tert-butyl 7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (5 g, crude) as a yellow oil. MS (ESI) *m/z* 438.2 $[M+H]^+$.

Step 2: methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000811] A mixture of tert-butyl 7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (1.6 g, 3.66 mmol, 1 *eq*) in HCl/MeOH (20 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.3 g, crude) as a yellow solid.

Step 3: methyl (2S)-2-[[6-(6-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000812] To a mixture of methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.3 g, 3.85 mmol, 1 *eq*) and 6-chloro-1H-indole-2-carboxylic acid (904.35 mg, 4.62 mmol, 1.2 *eq*) in DCM (9 mL) and DMF (3 mL) was added DMAP (1.41 g, 11.56 mmol, 3 *eq*) and EDCI (1.48 g, 7.71 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (25 mL * 3). The combined organic layers were washed with brine (20 mL * 1), dried over with Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3/1 to 0/1) to give methyl (2S)-2-[[6-(6-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.2 g, 2.21 mmol, 57.45% yield, 95% purity) as a yellow oil. MS (ESI) *m/z* 515.3 $[M+H]^+$

Step 4: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(6-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000813] A mixture of methyl (2S)-2-[[6-(6-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.2 g, 2.33 mmol, 1 *eq*) in NH_3/MeOH (7 M, 15 mL, 45.06 *eq*) was stirred at 50 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(6-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (980 mg, 1.96 mmol, 84.12% yield) as a yellow solid. MS (ESI) *m/z* 500.2 $[M+H]^+$.

Step 5: 6-(6-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide

[000814] To a mixture of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6-(6-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (980 mg, 1.96 mmol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (1.87 g, 7.84 mmol, 4 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition; column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-50%,10min) to afford 6-(6-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide (600 mg, 1.24 mmol, 63.51% yield) as a white solid. MS (ESI) *m/z* 482.2 $[M+H]^+$

Step 6: 6-(6-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide

[000815] The white solid was separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 60%-60%,min) to give 6-(6-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide (140 mg, 290.47 umol, 23.33% yield) and 6-(6-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide (110 mg, 228.23 umol, 18.33% yield) as a white solid. MS (ESI) *m/z* 482.2 $[M+H]^+$.

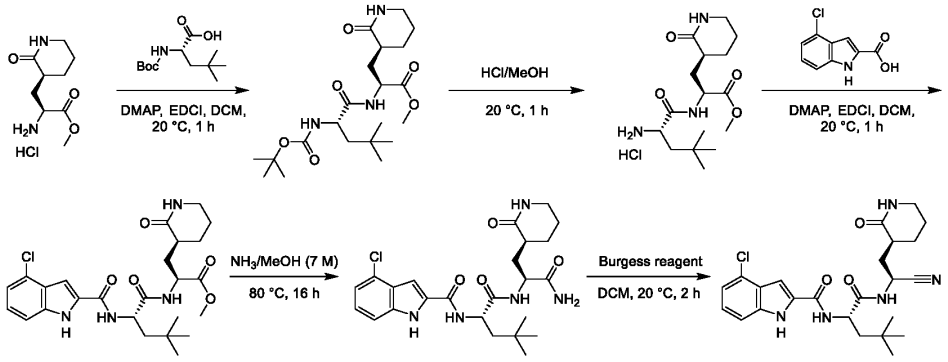
[000816] ^1H NMR (400MHz, DMSO-d_6) δ = 11.41 (br s, 1H), 8.60 (br s, 1H), 7.65 (br d, *J*=8.3 Hz, 1H), 7.49 (s, 1H), 7.24 - 6.88 (m, 3H), 5.10 - 4.82 (m, 1H), 4.56 (br s, 1H), 4.02 - 3.86 (m, 2H), 3.09 (br s, 2H), 2.36 - 2.26 (m, 1H), 2.25 - 2.07 (m, 3H), 2.07 - 1.77 (m, 8H), 1.73 - 1.32 (m, 3H).

[000817] ^1H NMR (400MHz, METHANOL-d_4) δ = 7.70 - 7.53 (m, 1H), 7.46 (s, 1H), 7.15 - 6.63 (m, 2H), 5.02 (dd, *J*=6.0, 10.6 Hz, 1H), 4.65 - 4.52 (m, 1H), 4.17 - 3.74 (m, 2H), 3.25 - 2.90 (m, 2H), 2.56 - 2.13 (m, 4H), 2.11 - 1.74 (m, 8H), 1.72 - 0.99 (m, 3H).

[000818] ^1H NMR (400MHz, DMSO-d_6) δ = 11.42 (br s, 1H), 8.66 (br s, 1H), 7.64 (br s, 1H), 7.49 (br s, 1H), 7.32 - 6.79 (m, 3H), 4.97 (br s, 1H), 4.57 (br s, 1H), 3.93 (br s, 2H), 3.11 (br s, 2H), 2.38 - 2.11 (m, 4H), 2.05 - 1.77 (m, 8H), 1.73 - 1.34 (m, 3H).

[000819] ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.64 (d, *J*=8.6 Hz, 1H), 7.55 - 7.42 (m, 1H), 7.13 - 6.99 (m, 2H), 5.09 (dd, *J*=6.3, 10.7 Hz, 1H), 4.55 (t, *J*=7.5 Hz, 1H), 4.12 - 3.95 (m, 2H), 3.27 - 3.17 (m, 2H), 2.63 - 2.36 (m, 3H), 2.13 - 1.90 (m, 9H), 1.80 (br s, 2H), 1.51 (br d, *J*=9.3 Hz, 1H).

Example 86. Synthesis of viral protease inhibitor compound 793



Step 1: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000820] To a solution of (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (4.97 g, 20.28 mmol, 1.2 *eq*) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (4 g, 16.90 mmol, 1 *eq*, HCl) in DCM (60 mL) was added DMAP (6.19 g, 50.70 mmol, 3 *eq*), and then EDCI (6.48 g, 33.80 mmol, 2 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the mixture was quenched by H_2O (50 mL), extracted with DCM (40 mL * 3), then was washed with 1M HCl (40 mL) and was extracted with DCM (80 mL * 3), and then was dried by NaCl (100 mL), then was concerntration in vacuum. The crude product was purified by column (Plate1, SiO_2, petroleum ether:ethyl acetate = 2:1 to 0:1, I_2, Rf = 0.22), then was concentrated in vacuum to afford methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (5.75 g, 11.43 mmol, 67.65% yield, 85% purity) as a white solid. MS (ESI) *m/z* 428.3 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000821] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 1.17 mmol, 1 *eq*) in

HCl/MeOH (10 mL) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (425 mg, crude, HCl) as a white solid. MS (ESI) *m/z* 328.2 $[M+H]^+$

Step 3 : *methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate*

[000822] To a solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (409.27 mg, 1.12 mmol, 1 *eq*, HCl) and 4-chloro-1H-indole-2-carboxylic acid (220 mg, 1.12 mmol, 1 *eq*) in DCM (15 mL) was added EDCI (646.84 mg, 3.37 mmol, 3 *eq*), and then was added DMAP (412.22 mg, 3.37 mmol, 3 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was poured into H_2O (50 mL) at 20 °C, and extracted with DCM (20 mL * 3). The combined organic layers were washed with 1M HCl (20 mL * 2), and then was dried by NaCl (10 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (321 mg, 572.07 umol, 50.86% yield, 90% purity) as a white solid. MS (ESI) *m/z* 505.2 $[M+H]^+$.

Step 4: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-chloro-1H-indole-2-carboxamide

[000823] A solution of methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (306 mg, 605.93 umol, 1 *eq*) in NH_3/MeOH (7 M, 3 mL, 34.66 *eq*) was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-chloro-1H-indole-2-carboxamide (250 mg, crude) as a yellow solid. MS (ESI) *m/z* 490.2 $[M+H]^+$.

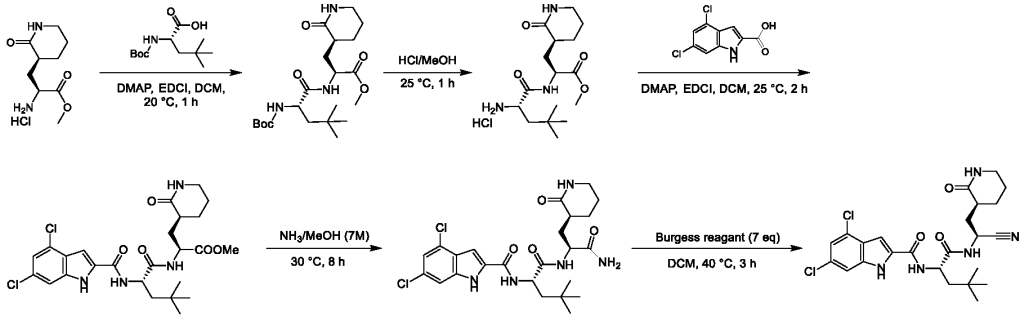
Step 5: 4-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1H-indole-2-carboxamide

[000824] To a solution of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-chloro-1H-indole-2-carboxamide (230 mg, 469.39 umol, 1 *eq*) in DCM (3 mL) was added Burgessreagent

(335.58 mg, 1.41 mmol, 3 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give 4-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1H-indole-2-carboxamide (114 mg, 241.54 umol, 51.46% yield, 100% purity) as a white solid. MS (ESI) *m/z* 472.2 $[M+H]^+$.

[000825] 1H NMR (400MHz, MeOD-d_4) δ = 7.39 (d, *J* = 8.4Hz, 1H), 7.28 (s, 1H), 7.18 (t, *J* = 7.8Hz, 1H), 7.12 - 7.04 (m, 1H), 7.09 (d, *J* = 7.4Hz, 1H), 5.16 - 5.02 (m, 1H), 4.65 (d, *J* = 4.4, 8.4Hz, 1H), 3.24 - 3.16 (m, 2H), 2.49 - 2.38 (m, 2H), 2.00 - 1.73 (m, 5H), 1.66 (d, *J* = 8.4Hz, 1H), 1.55 - 1.45 (m, 1H), 1.03 (s, 8H)

Example 87. Synthesis of viral protease inhibitor compound 795



Step 1: (S)-methyl2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000826] To a solution of (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (4.97 g, 20.28 mmol, 1.2 *eq*) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (4 g, 16.90 mmol, 1 *eq*, HCl) in DCM (120 mL) was added DMAP (6.19 g, 50.70 mmol, 3 *eq*), and then was added EDCI (6.48 g, 33.80 mmol, 2 *eq*). The resulting mixture was stirred at 20 °C for 1 h. Upon completion, The mixture was quenched by H_2O (500 mL) and was extracted with DCM (200 mL * 3), then was washed with 1M HCl (200 mL) and was extracted with DCM (80 mL * 3), and then was dried by NaCl (100 mL), then was concentrated in vacuum. The crude product was purified by column (Plate1, SiO_2, petroleum ether:ethyl acetate = 2:1 to 0:1, I_2, Rf = 0.22), then was concentrated in vacuum to give (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (5.75 g, 11.43 mmol, 67.65% yield, 85% purity) as a white solid. MS (ESI) *m/z* 428.3 $[M+H]^+$.

Step 2: (S)-methyl2-((S)-2-amino-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000827] A solution of (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (700 mg, 1.64 mmol, 1 *eq*) in HCl/MeOH (10 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction was concentrated in the vacuum to give (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (630 mg, crude, HCl) as yellow solid. MS (ESI) *m/z* 328.2 $[M+H]^+$.

Step 3: (S)-methyl 2-((S)-2-(4,6-dichloro-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000828] To a solution of (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (630 mg, 1.73 mmol, 1 *eq*, HCl) in DCM (20 mL) was added 4,6-dichloro-1H-indole-2-carboxylic acid (438.12 mg, 1.90 mmol, 1.1 *eq*), DMAP (634.54 mg, 5.19 mmol, 3 *eq*), and EDCI (431.47 mg, 2.25 mmol, 1.3 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was quenched by addition H_2O (100 mL) and then extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure and purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 7/3 to 0/1) to give product (*S*)-methyl 2-((*S*)-2-(4,6-dichloro-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (400 mg, 595.42 umol, 34.39% yield, 80.3% purity) as yellow solid. MS (ESI) *m/z* 539.2 $[M+H]^+$.

Step 4: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4,6-dichloro-1H-indole-2-carboxamide

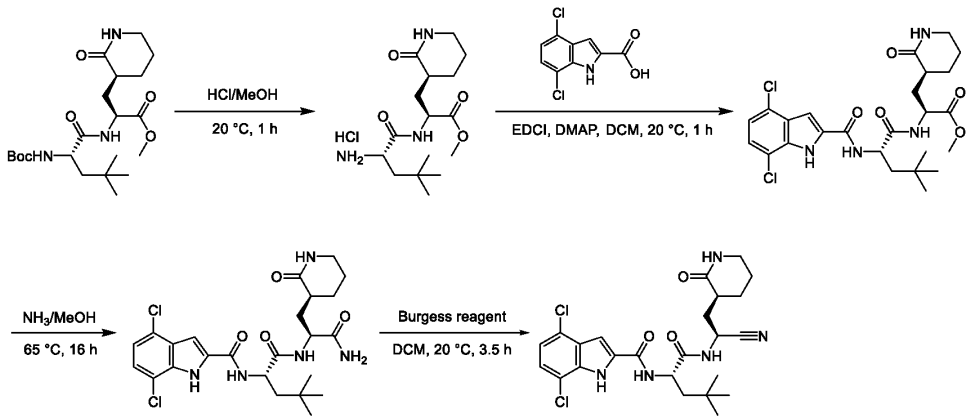
[000829] A solution of (*S*)-methyl 2-((*S*)-2-(4,6-dichloro-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (370 mg, 685.88 umol, 1 *eq*) in NH_3 (7 M, 20 mL, 204.12 *eq*) was stirred at 30 °C for 8 h. Upon completion, the reaction was concentrated in the vacuum to afford product N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4,6-dichloro-1H-indole-2-carboxamide (340 mg, crude) was yellow solid. MS (ESI) *m/z* 524.2 $[M+H]^+$.

Step5: 4,6-dichloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-1H-indole-2-carboxamide

[000830] To a solution of N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4,6-dichloro-1H-indole-2-carboxamide (320 mg, 610.18 umol, 1 *eq*) in DCM (15 mL) was added Burgess reagent (1.02 g, 4.27 mmol, 7 *eq*), and the mixture was stirred at 40 °C for 3 h. Upon completion, the reaction was concentrated in the vacuum and purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%:40%-60%,8min) to afford 4,6-dichloro-N-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-1H-indole-2-carboxamide (110 mg, 217.21 umol, 35.60% yield, 100% purity) as a white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$

[000831] ^1H NMR (400MHz, DMSO-d_6) δ = 12.00 (br s, 1H), 8.94 - 8.92 (m, 1H), 8.81 - 8.80 (m, 1H), 7.52 (br s, 1H), 7.42 (s, 2H), 7.24 (s, 1H), 5.11 - 4.98 (m, 1H), 4.54 - 4.49 (m, 1H), 3.12 - 3.01 (m, 2H), 2.34 - 2.19 (m, 2H), 1.85 - 1.63 (m, 5H), 1.58 - 1.45 (m, 1H), 1.43 - 1.32 (m, 1H), 0.94 (s, 9H)

Example 88. Synthesis of viral protease inhibitor compound 797



Step 1: (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000832] A mixture of methyl (2*S*)-2-[[(2*S*)-2-(*tert*-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (800 mg, 1.87 mmol, 1 *eq*) and

HCl/MeOH (4 M, 25 mL, 53.44 *eq*) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2*S*)-2-[[(2*S*)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (650 mg, crude, HCl) as a white solid. MS (ESI) *m/z* 328.2 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-2-[(4,7-dichloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000833] A mixture of methyl (2*S*)-2-[[(2*S*)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (650 mg, 1.79 mmol, 1.2 *eq*, HCl), 4,7-dichloro-1*H*-indole-2-carboxylic acid (342.45 mg, 1.49 mmol, 1 *eq*), EDCI (856.10 mg, 4.47 mmol, 3 *eq*) and DMAP (545.57 mg, 4.47 mmol, 3 *eq*) in DCM (10 mL) was stirred at 20 °C for 1 h. Upon completion, the mixture was added H_2O (50 mL) and then extracted with ethyl acetate (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 10:1) to afford methyl (2*S*)-2-[[(2*S*)-2-[(4,7-dichloro-1*H*-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (650 mg, 1.17 mmol, 78.79% yield, 97.34% purity) as a white solid. MS (ESI) *m/z* 539.2 $[M+H]^+$.

Step 3: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4,7-dichloro-1H-indole-2-carboxamide

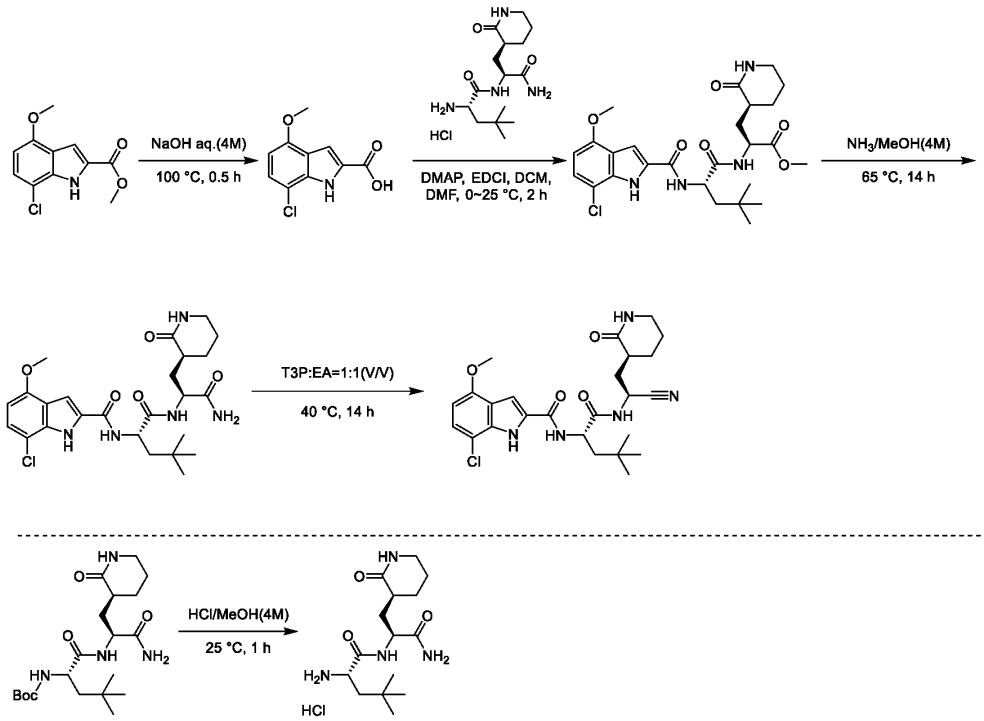
[000834] A mixture of methyl (2S)-2-[[(2S)-2-[(4,7-dichloro-1*H*-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (620 mg, 1.15 mmol, 1 *eq*) and NH_3/MeOH (7 M, 20 mL, 121.81 *eq*) was stirred at 65 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure to give the product *N*-[(1*S*)-1-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4,7-dichloro-1*H*-indole-2-carboxamide (550 mg, crude) as a white solid. MS (ESI) *m/z* 524.2 $[M+H]^+$.

Step 4: 4,7-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000835] A mixture of *N*-[(1*S*)-1-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4,7-dichloro-1*H*-indole-2-carboxamide (530 mg, 1.01 mmol, 1 *eq*) and Burgess reagent (722.50 mg, 3.03 mmol, 3 *eq*) in DCM (10 mL) was stirred at 20 °C for 3.5 h. Upon completion, the mixture was concentrated under reduced pressure to give the residue. Then the residue was purified by prep-HPLC (column: Kromasil C18 (250 * 50 mm * 10 um); mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 45% - 75%, 10 min) to afford 4,7-dichloro-*N*-[(1*S*)-1-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1*H*-indole-2-carboxamide (170 mg, 334.61 umol, 33.11% yield, 99.68% purity) as a white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$.

[000836] ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.62 - 7.56 (m, 1H), 7.52 - 7.46 (m, 1H), 7.21 - 7.14 (m, 1H), 5.14 - 5.07 (m, 1H), 4.70 - 4.64 (m, 1H), 3.25 - 3.17 (m, 2H), 2.51 - 2.38 (m, 2H), 2.02 - 1.85 (m, 3H), 1.85 - 1.61 (m, 3H), 1.58 - 1.44 (m, 1H), 1.08 - 1.02 (m, 9H)

Example 89. Synthesis of viral protease inhibitor compound 799



Step 1: 7-chloro-4-methoxy-1H-indole-2-carboxylic acid

[000837] A mixture of methyl 7-chloro-4-methoxy-1H-indole-2-carboxylate (500 mg, 2.09 mmol, 1 *eq*) in NaOH (2 M, 10.43 mL, 10 *eq*) was then stirred at 100 °C for 0.5 h. Upon completion, the mixture was acidified by HCl (3M) to adjust the pH to about 3, and then the reaction was extracted with EtOAc (10 mL* 3). The organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure to give 7-chloro-4-methoxy-1H-indole-2-carboxylic acid (400 mg, crude) as a yellow solid.

Step 2: (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide

[000838] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (800 mg, 1.87 mmol, 1 eq) in HCl/MeOH (4 M, 8 mL, 17.10 eq) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide (810 mg, crude, HCl) as a white solid.

Step 3: (S)-methyl 2-((S)-2-(7-chloro-4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000839] To a solution of 7-chloro-4-methoxy-1H-indole-2-carboxylic acid (440 mg, 1.95 mmol, 1 *eq*) in DCM (8 mL) and DMF (4 mL) was added (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide (851.53 mg, 2.34 mmol, 1.2 *eq*, HCl), DMAP (714.74 mg, 5.85 mmol, 3 *eq*), and then was added EDCI (747.67 mg, 3.90 mmol, 2 *eq*) at 0 °C. The mixture was then stirred at 25 °C for 2 h. Upon completion, the mixture was quenched with water (20 mL) and extracted with DCM (10 mL* 3). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 100:1 to 10:1) to give (S)-methyl 2-((S)-2-(7-chloro-4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1.3 g, 1.82 mmol, 93.45% yield, 75% purity) as yellow solid. MS (ESI) *m/z* 535.1 $[M+H]^+$.

Step 4: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-4-methoxy-1H-indole-2-carboxamide

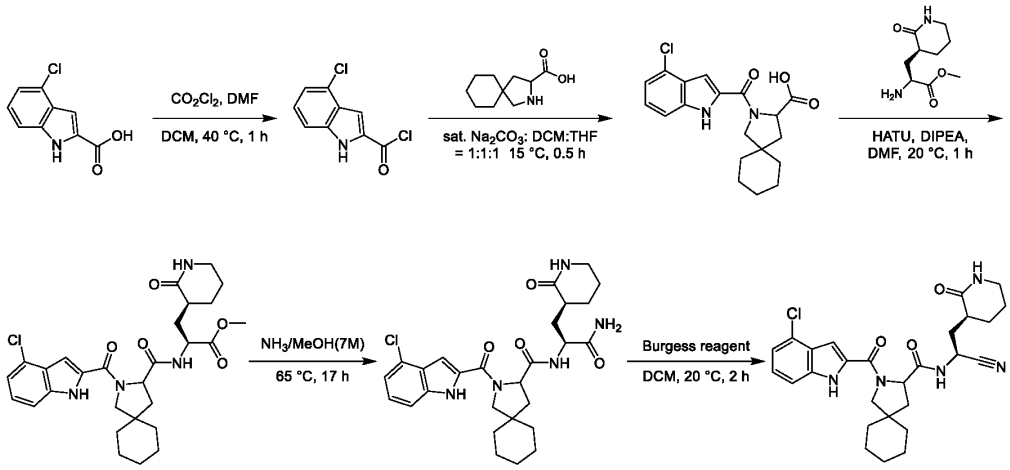
[000840] A solution of (S)-methyl 2-((S)-2-(7-chloro-4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1.3 g, 1.82 mmol, 75% purity, 1 *eq*) in NH_3/MeOH (7 M, 15 mL, 57.62 *eq*) was stirred at 65°C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-4-methoxy-1H-indole-2-carboxamide (1.25 g, crude) as a yellow solid. MS (ESI) *m/z* 520.3 $[M+H]^+$.

Step 5: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000841] To a mixture of N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-4-methoxy-1H-indole-2-carboxamide (1.21 g, 1.75 mmol, 75% purity, 1 *eq*) in EtOAc (6 mL) was added T3P (6.42 g, 10.09 mmol, 6 mL, 50% purity, 5.78 eq), and then the reaction was stirred at 40 °C for 14 h. Upon completion, the mixture was quenched with water (20 mL) and extracted with EtOAc (10 mL* 3). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250* 50mm* 10 um);mobile phase: [water (10 mM NH_4HCO_3)- ACN]; B%: 30% - 60%, 10 min) to give 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (496.09 mg, 988.22 umol, 56.63% yield, 100% purity) as a white solid. MS (ESI) *m/z* 502.2 $[M+H]^+$.

[000842] ^1H NMR (400MHz, DMSO-d_6) δ = 11.64 (br s, 1H), 9.12 - 8.90 (m, 1H), 8.72 - 8.54 (m, 1H), 7.52 (br s, 1H), 7.28 (s, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 5.05 (q, *J* = 8.0 Hz, 1H), 4.62 - 4.50 (m, 1H), 3.89 (s, 3H), 3.07 (br s, 2H), 2.31 - 2.15 (m, 2H), 1.88 - 1.63 (m, 5H), 1.60 - 1.33 (m, 2H), 1.06 - 0.85 (m, 9H).

Example 90. Synthesis of viral protease inhibitor compound 801



Step 1: 4-chloro-1H-indole-2-carbonyl chloride

[000843] A solution of 4-chloro-1H-indole-2-carboxylic acid (600 mg, 3.07 mmol, 1 eq) in DCM (9 mL) was added DMF (6.73 mg, 92.02 umol, 7.08 uL, 0.03 eq) and $(COCl)_2$ (778.70 mg, 6.13 mmol, 537.04 uL, 2 eq) was stirred at 40 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give 4-chloro-1H-indole-2-carbonyl chloride (655 mg, crude) was obtained as a yellow oil.

Step 2: 2-(4-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid

[000844] A mixture of 4-chloro-1H-indole-2-carbonyl chloride (655 mg, 3.06 mmol, 1.1 eq) in THF (6 mL) DCM (6 mL) was poured into a mixture of 2-azaspiro[4.5]decane-3-carboxylic acid (611.20 mg, 2.78 mmol, 1 eq, HCl), Na_2CO_3 (884.85 mg, 2.78 mmol, 3 eq) in DCM (6 mL) and H_2O (6 mL). The mixture was stirred at 15 °C for 0.5 h under N_2 atmosphere. Upon completion, the reaction mixture was quenched by addition HCl (1M) (15 mL) and extracted with DCM (10 mL * 4). The combined organic layers were concentrated under reduced pressure to give a residue. The crude product was triturated with EtOAc (3 mL) at 20 °C for 15 min. to give 2-(4-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (710 mg, 1.97 mmol, 70.73% yield) was obtained as white solid. MS (ESI) m/z 361.2 $[M+H]^+$.

Step 3: (2S)-methyl 2-(2-(4-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000845] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (512.31 mg, 2.16 mmol, 1.1 eq, HCl) 2-(4-chloro-1H-indole-2-carbonyl)-2-

azaspiro[4.5]decane-3-carboxylic acid (710 mg, 1.97 mmol, 1 eq) in DMF (15 mL) was added DIPEA (762.90 mg, 5.90 mmol, 1.03 mL, 3 eq) and HATU (748.17 mg, 1.97 mmol, 1 eq). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (40 mL), and then extracted with ethyl acetate (20 mL * 4). The combined organic layers were washed with brine (20 mL *1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give methyl (2S)-2-[[2-(4-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (850 mg, 1.57 mmol, 79.55% yield) as a yellow oil.

Step 4: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(4-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000846] A solution of methyl (2S)-2-[[2-(4-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (850 mg, 1.57 mmol, 1 eq) in MeOH/NH_3 (7 M, 11.05 mL, 49.42 eq) was stirred at 65 °C for 17 h. Upon completion, The reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (820 mg, crude) was obtained as colorless oil. MS (ESI) m/z 528.3 $[M+H]^+$.

Step 5: 2-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[000847] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (820 mg, 1.55 mmol, 1 eq) in DCM (15 mL) was added Burgess reagent (999.20 mg, 4.19 mmol, 2.7 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (3 mL) and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 45%-75%,10min) to give desired compound (450 mg) as a white solid, which was further separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 60%-60%,min) to afford 2-(4-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-

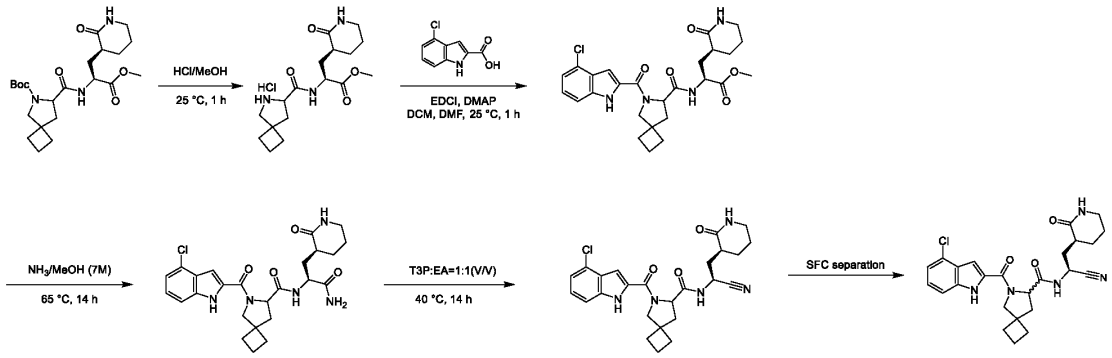
piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (168.83 mg, 331.02 umol, 21.32% yield, 100% purity) as white solid. MS (ESI) m/z 510.3 $[M+H]^+$.

[000848] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.72 (br s, 1 H) 8.52 - 9.07 (m, 1 H) 6.72 - 7.49 (m, 5 H) 4.81 - 5.16 (m, 1 H) 4.43 - 4.78 (m, 1 H) 3.51 - 3.92 (m, 2 H) 2.10 - 2.39 (m, 3 H) 1.25 - 1.98 (m, 16 H).

[000849] To give 2-(4-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (180.55 mg, 354.00 umol, 22.80% yield, 100% purity) was obtained as white solid. MS (ESI) m/z 510.3 $[M+H]^+$.

[000850] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.56 - 11.85 (m, 1 H) 8.45 - 8.94 (m, 1 H) 7.43 (br d, J = 8.16 Hz, 1 H) 7.04 - 7.35 (m, 3 H) 6.75 - 7.03 (m, 1 H) 4.42 - 5.12 (m, 2 H) 3.58 - 3.91 (m, 2 H) 2.06 - 2.30 (m, 3 H) 1.21 - 1.94 (m, 16 H).

Example 91. Synthesis of viral protease inhibitor compound 803



Step 1: (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(6-azaspiro[3.4]octane-7-carboxamido)propanoate

[000851] A solution of tert-butyl 7-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate (1.2 g, 2.47 mmol, 90% purity, 1 *eq*) in HCl/MeOH (4 M, 12 mL, 19.45 *eq*) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(6-azaspiro[3.4]octane-7-carboxamido)propanoate (1.3 g, crude, HCl) as a yellow solid. MS (ESI) *m/z* 338.2 $[M+H]^+$.

Step 2: (2S)-methyl 2-(6-(4-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000852] To a solution of (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(6-azaspiro[3.4]octane-7-carboxamido)propanoate (1.25 g, 2.34 mmol, 70% purity, 1 *eq*, HCl) in DCM (8 mL) and DMF (4 mL) was added 4-chloro-1H-indole-2-carboxylic acid (457.78 mg, 2.34 mmol, 1 *eq*), DMAP (857.77 mg, 7.02 mmol, 3 *eq*), and then was added EDCI (897.29 mg, 4.68 mmol, 2 *eq*). The mixture was then stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with DCM (10 mL * 3). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, dichloromethane:methanol = 100:1 to 10:1) to give (2S)-methyl 2-(6-(4-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1.51 g, 2.20 mmol, 93.96% yield, 75% purity) as a yellow solid. MS (ESI) *m/z* 515.2 $[M+H]^+$.

Step 3: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-6-(4-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000853] A solution of (2S)-methyl 2-(6-(4-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1.51 g, 2.20 mmol, 75% purity, 1 *eq*) in NH_3/MeOH (7 M, 15 mL, 47.75 *eq*) was stirred at 65 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-6-(4-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (1.5 g, crude) as a yellow solid. MS (ESI) *m/z* 500.3 $[M+H]^+$.

Step 4: 6-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide

[000854] To a solution of N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-6-(4-chloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (1.5 g, 2.10 mmol, 70% purity, 1 *eq*) in EtOAc (8 mL) was added T3P (8.56 g, 13.45 mmol, 8 mL, 50% purity, 6.41 *eq*), and then the reaction was stirred at 40 °C for 14 h. Upon completion, the mixture was quenched with water (25 mL) and extracted with EtOAc (15 mL * 3). The organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered,

and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250* 50mm* 10 um); mobile phase:[water (10 mM NH_4HCO_3)-ACN]; B%: 30%-50%, 10min) to give 6-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide (420 mg, 865.32 umol, 41.20% yield, 99.3% purity) as a white solid. MS (ESI) *m/z* 482.2 $[M+H]^+$.

Step 5: 6-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide

[000855] 6-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide (420 mg, 99.3% purity) was separation by SFC (column: REGIS(S,S)WHELK-O1(250 mm* 25 mm, 10 um); mobile phase: [0.1% NH_3H_2O EtOH]; B%: 60%-60%, min) to give 6-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 1 (8.72 mg, 18.09 umol, 2.09% yield, 100% purity) as a white solid. MS (ESI) *m/z* 482.2 $[M+H]^+$.

[000856] ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.49 - 7.34 (m, 1H), 7.20 (br t, J=7.5 Hz, 1H), 7.15 - 6.67 (m, 2H), 5.15 - 5.00 (m, 1H), 4.65 - 4.54 (m, 1H), 4.15 - 3.78 (m, 2H), 3.25 - 2.99 (m, 2H), 2.58 - 1.25 (m, 15H).

[000857] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.96 (br s, 1H), 9.06 - 8.67 (m, 1H), 7.53 (br d, J=11.2 Hz, 1H), 7.43 (br d, J=7.7 Hz, 1H), 7.27 - 7.05 (m, 2H), 7.04 - 6.54 (m, 1H), 5.06 - 4.86 (m, 1H), 4.57 - 4.36 (m, 1H), 4.18 - 3.66 (m, 2H), 3.08 (br s, 2H), 2.37 - 2.11 (m, 4H), 2.07 - 1.17 (m, 11H).

[000858] To give 6-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 2 (197.12 mg, 408.99 umol, 47.26% yield, 100% purity) as a white solid. MS (ESI) *m/z* 482.2 $[M+H]^+$.

[000859] ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.46 - 7.34 (m, 1H), 7.25 - 7.18 (m, 1H), 7.17 - 6.65 (m, 2H), 5.08 - 4.97 (m, 1H), 4.58 (t, J = 7.5 Hz, 1H), 4.22 - 3.72 (m, 2H), 3.24 - 2.87 (m, 2H), 2.53 - 2.18 (m, 4H), 2.13 - 1.75 (m, 8H), 1.70 - 1.22 (m, 3H).

[000860] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.95 (s, 1H), 9.30 - 8.55 (m, 1H), 7.58 - 7.32 (m, 2H), 7.31 - 7.07 (m, 2H), 7.05 - 6.55 (m, 1H), 5.16 - 4.85 (m, 1H), 4.47 (t, J = 7.2 Hz, 1H), 4.13 - 3.68 (m, 2H), 3.17 - 2.82 (m, 2H), 2.34 - 2.10 (m, 4H), 2.10 - 1.67 (m, 9H), 1.63 - 1.01 (m, 2H).

[000861] To give 6-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 3 (111.90 mg, 232.17 umol, 26.83% yield, 100% purity) as a white solid. MS (ESI) m/z 482.2 $[M+H]^+$.

[000862] ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.43 - 7.34 (m, 1H), 7.22 - 7.16 (m, 1H), 7.13 - 6.73 (m, 2H), 5.10 (dd, J = 5.7, 10.3 Hz, 1H), 4.57 (t, J = 7.9 Hz, 1H), 4.16 - 3.97 (m, 2H), 3.27 - 3.19 (m, 2H), 2.63 - 2.33 (m, 3H), 2.30 - 2.19 (m, 1H), 2.11 - 1.92 (m, 8H), 1.85 - 1.68 (m, 2H), 1.55 - 1.47 (m, 1H).

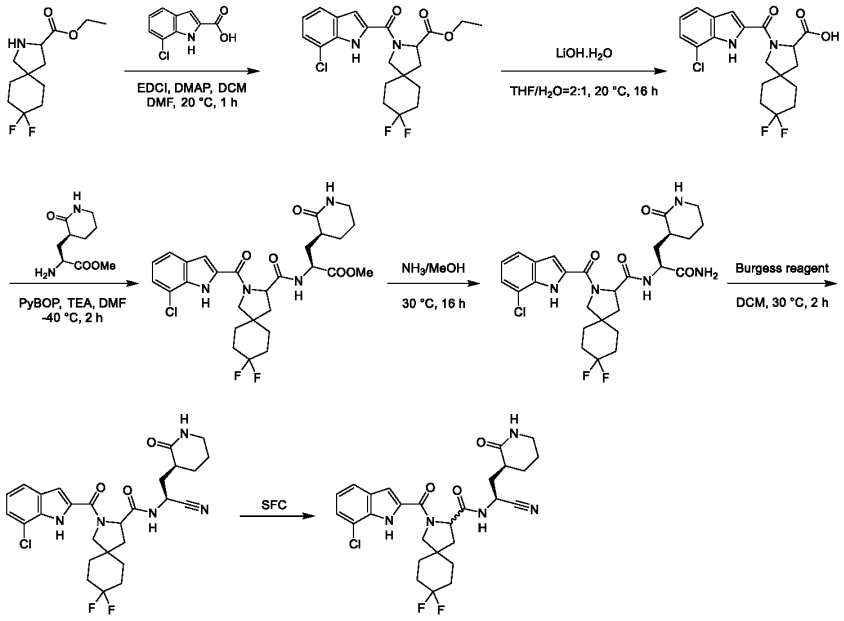
[000863] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.95 (br s, 1H), 9.43 - 8.64 (m, 1H), 7.63 - 7.33 (m, 2H), 7.27 - 7.05 (m, 2H), 7.04 - 6.56 (m, 1H), 5.10 - 4.86 (m, 1H), 4.46 (br t, J = 7.4 Hz, 1H), 4.08 - 3.60 (m, 2H), 3.18 - 2.88 (m, 2H), 2.36 - 2.09 (m, 4H), 2.04 - 1.17 (m, 11H).

[000864] To give 6-(4-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 4 (2.11 mg, 4.24 umol, 0.49% yield, 96.8% purity) as a white solid. MS (ESI) m/z 482.2 $[M+H]^+$.

[000865] ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.44 - 7.36 (m, 1H), 7.24 - 7.17 (m, 1H), 7.16 - 6.69 (mz, 2H), 5.21 - 5.01 (m, 1H), 4.68 - 4.51 (m, 1H), 4.12 - 3.81 (m, 2H), 3.25 - 3.19 (m, 2H), 2.56 - 2.15 (m, 3H), 2.12 - 1.69 (m, 8H), 1.64 - 1.26 (m, 4H).

[000866] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.96 (br s, 1H), 9.02 - 8.65 (m, 1H), 7.62 - 7.46 (m, 1H), 7.45 - 7.34 (m, 1H), 7.27 - 7.06 (m, 2H), 7.04 - 6.57 (m, 1H), 5.04 - 4.86 (m, 1H), 4.57 - 4.37 (m, 1H), 4.10 - 3.63 (m, 2H), 3.17 - 2.83 (m, 2H), 2.34 - 2.26 (m, 2H), 2.23 - 2.10 (m, 2H), 2.04 - 1.82 (m, 7H), 1.80 - 1.37 (m, 2H), 1.37 - 1.13 (m, 2H).

Example 92. Synthesis of viral protease inhibitor compound 805



Step 1: ethyl 2-(7-chloro-1H-indole-2-carbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxylate

[000867] To a solution of ethyl 8,8-difluoro-2-azaspiro[4.5]decane-3-carboxylate (1.5 g, 6.07 mmol, 1 *eq*) and 7-chloro-1*H*-indole-2-carboxylic acid (1.42 g, 7.28 mmol, 1.2 *eq*) in DCM (25 mL) was added DMAP (1.48 g, 12.13 mmol, 2 *eq*) and EDCI (2.33 g, 12.13 mmol, 2 *eq*), then the mixture was stirred at 20 °C for 2 h. Upon the reaction completement, the mixture was quenched by water (20 mL) and was extracted with DCM (10 mL * 3), then was concentrated in vacuum and was purified by column (SiO_2, petroleum ether:ethyl acetate = 20:1 to 2.5:1) to obtained ethyl 2-(7-chloro-1*H*-indole-2-carbonyl)-8, 8-difluoro-2-azaspiro[4.5] decane-3-carboxylate (1.6 g, 3.58 mmol, 58.98% yield, 95% purity) as a pink oil. MS (ESI) *m/z* 425.2 $[M+H]^+$.

Step 2: 2-(7-chloro-1H-indole-2-carbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxylic acid

[000868] To a solution of ethyl 2-(7-chloro-1*H*-indole-2-carbonyl)-8, 8-difluoro-2-azaspiro [4.5] decane-3-carboxylate (1.6 g, 3.77 mmol, 1 *eq*) in THF (12 mL) and H_2O (6 mL) was added $LiOH.H_2O$ (474.09 mg, 11.30 mmol, 3 *eq*), and then the mixture was stirred at 20 °C for 16 h. Upon completion, the mixture was concentrated in vacuum and the pH was adjusted to pH=~1 with 1M HCl (30 mL). The reaction was triturated by DCM (30 mL), and then was filtered and the filtered cake was dried in vacuum to obtain

2-(7-chloro-1*H*-indole-2-carbonyl)-8,8-difluoro-2-azaspiro[4.5]decane -3-carboxylic acid (1.4 g, 3.53 mmol, 93.69% yield) as a white solid.

Step 3:
(2S)-methyl2-(2-(7-chloro-1H-indole-2-carbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000869] To a solution of 2-(7-chloro-1*H*-indole-2-carbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxylic acid (1.7 g, 4.28 mmol, 1 *eq*) and methyl (2*S*)-2-amino-3-[(3*S*)-2-oxo-3-piperidyl] propanoate (1.01 g, 4.28 mmol, 1 *eq*, HCl) in DMF (30 mL) was added PyBOP (2.23 g, 4.28 mmol, 1 *eq*), and then was added TEA (1.30 g, 12.85 mmol, 1.79 mL, 3 *eq*) in DMF (5 mL) at -40 °C. The mixture was stirred at -40 °C for 2 h. Upon the reaction completion, the mixture was poured into water (100 mL) and was extracted with DCM (40 mL * 3), then was dried by Na_2SO_4 and was concentrated in vacuum and was purified by column (SiO_2, petroleum ether:ethyl acetate = 1:1 to DCM:MeOH = 10:1) to obtained (2*S*)-methyl 2-(2-(7-chloro-1*H*-indole-2-carbonyl)-8, 8-difluoro-2-azaspiro [4.5] decane-3-carboxamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (2.2 g, 3.04 mmol, 70.95% yield, 80% purity) as a colorless solid. MS (ESI) *m/z* 579.3 $[M+H]^+$.

Step 4: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(7-chloro-1H-indole-2-carbonyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxamide

[000870] A solution of (2*S*)-methyl 2-(2-(7-chloro-1*H*-indole-2-carbonyl)-8,8-difluoro-2-azaspiro [4.5] decane-3-carboxamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (400 mg, 518.10 umol, 75% purity, 1 *eq*) in NH_3/MeOH (6 mL, 7M) was stirred at 30 °C for 16 h. Upon the reaction completion, the mixture was concentrated in vacuum to obtain *N*-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2 -yl)-2-(7-chloro-1*H*-indole-2-carbonyl) -8, 8-difluoro-2-azaspiro[4.5]decane-3-carboxamide (1.4 g, batch 5, crude) as a white solid. MS (ESI) *m/z* 564.2 $[M+H]^+$

Step 5: 2-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxamide

[000871] To a solution of *N*-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl)-2-(7-chloro -1*H*-indole-2-carbonyl)-8,8-difluoro-2-azaspiro[4.5] decane-3-carboxamide (1.4 g, 2.48 mmol, 1 *eq*) in DCM (30 mL) was added Burgess reagent (1.77 g, 7.45 mmol,

3 *eq*). The mixture was stirred at 30 °C for 2 h. Upon the reaction completion, the reaction mixture was quenched with water (2 mL) and was dried by blowing N_2. The concentrate was purified by prep-HPLC (column: Welch Xtimate C18 250 * 70 mm#10um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 30%-60%, 20min) to obtain 2-(7-chloro-1*H*-indole-2-carbonyl)-*N*-((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxamide (740 mg, 1.33 mmol, 53.51% yield, 98% purity) as a white solid. MS (ESI) *m/z* 546.2 $[M+H]^+$

Step 6: 2-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxamide)

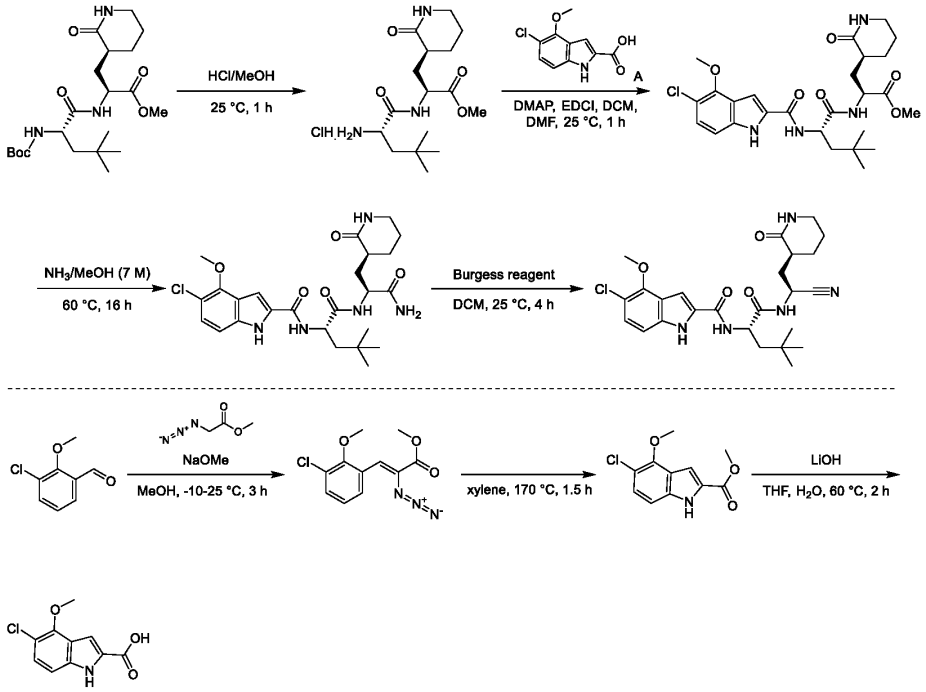
[000872] The 2-(7-chloro-1*H*-indole-2-carbonyl)-*N*-((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)-8,8 -difluoro-2-azaspiro[4.5]decane-3-carboxamide (740 mg, 1.33 mmol, 53.51% yield, 98% purity) was separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm, 10um); mobile phase: [Neu-ETOH]; B%: 60%-60%, 7min) to obtained 2-(7-chloro-1*H*-indole-2-carbonyl)-*N*-((*S*) -1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxamide (Isomer 1: 340 mg, 622.70 umol, 45.95% yield, 100% purity) as a white solid. MS (ESI) *m/z* 546.1 $[M+H]^+$

[000873] ^1H NMR (400MHz, MeOD-d_4) δ ppm 7.67 - 7.47 (m, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.18 - 6.82 (m, 2H), 5.15 - 4.97 (m, 1H), 4.82 - 4.58 (m, 1H), 4.05 - 3.73 (m, 2H), 3.27 - 2.92 (m, 2H), 2.63 - 2.44 (m, 2H), 2.39 (dd, *J* = 7.7, 12.5 Hz, 1H), 2.07 - 1.72 (m, 11H), 1.68 - 1.40 (m, 3H).

[000874] 2-(7-chloro-1*H*-indole-2-carbonyl)-*N*-((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)-8,8-difluoro-2-azaspiro[4.5]decane-3-carboxamide (Isomer 2: 325 mg, 595.23 umol, 43.92% yield, 100% purity) as a white solid. MS (ESI) *m/z* 546.2 $[M+H]^+$.

[000875] ^1H NMR (400MHz, MeOD-d_4) δ ppm 7.64 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.20 - 6.81 (m, 2H), 5.02 (dd, *J* = 6.2, 10.1 Hz, 1H), 4.66 (dd, *J* = 7.9, 9.4 Hz, 1H), 4.08 - 3.81 (m, 2H), 3.23 - 3.00 (m, 2H), 2.55 - 2.23 (m, 3H), 2.02 - 1.72 (m, 10H), 1.71 - 1.59 (m, 3H), 1.58 - 1.44 (m, 1H).

Example 93. Synthesis of viral protease inhibitor compound 806a



Step 1: methyl (Z)-2-azido-3-(3-chloro-2-methoxy-phenyl)prop-2-enoate

[00876] A solution of NaOMe (1.90 g, 35.17 mmol, 2 eq) in MeOH (20 mL) was cooled to -10 °C, and a mixture 3-chloro-2-methoxy-benzaldehyde (3 g, 17.59 mmol, 1 eq) and methyl azide acetate (4.12 g, 35.17 mmol, 2 eq) in MeOH (10 mL) was added drop-wise. The mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was quenched by addition H_2O 5(0 mL) at 0 °C, and then diluted with H_2O (30 mL) and extracted with ethyl acetate (100 mL, which extracted as 50 mL * 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 20/1 to 10/1) to afford (Z)-2-azido-3-(3-chloro-2-methoxy-phenyl)prop-2-enoate (2.1 g, 7.45 mmol, 42.38% yield, 95% purity) as a yellow solid.

Step 2: methyl 5-chloro-4-methoxy-1H-indole-2-carboxylate

[00877] Methyl (Z)-2-azido-3-(3-chloro-2-methoxy-phenyl)prop-2-enoate (2.1 g, 7.85 mmol, 1 eq) in xylene (20 mL), the mixture was stirred at 170 °C for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum

ether/ethyl acetate = 10/1 to 5/1) to get the compound methyl 5-chloro-4-methoxy-1H-indole-2-carboxylate (1.7 g, 6.38 mmol, 81.37% yield, 90% purity) as a white solid.

Step 3: 5-chloro-4-methoxy-1H-indole-2-carboxylic acid

[000878] To a mixture of methyl 5-chloro-4-methoxy-1H-indole-2-carboxylate (1.2 g, 5.01 mmol, 1 eq) in THF (20 mL) and H_2O (10 mL) was added LiOH.H_2O (420.24 mg, 10.01 mmol, 2 eq). The mixture was stirred at 60 °C for 2 h. Upon completion, the pH of the reaction mixture was adjusted to pH=3 by addition HCl, and then diluted with H_2O (30 mL). The reaction was extracted with ethyl acetate (50 mL * 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue 5-chloro-4-methoxy-1H-indole-2-carboxylic acid (0.95 g, 4.00 mmol, 79.88% yield, 95% purity) as a white solid.

Step 4: methyl (2S)-2-[[(2S)-2-[(5-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl- pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000879] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3- piperidyl]propanoate (468 mg, 1.29 mmol, 1 eq, HCl) and 5-chloro-4-methoxy-1H-indole-2- carboxylic acid (290.19 mg, 1.29 mmol, 1 eq) in DMF (10 mL) and DCM (20 mL) was added EDCI (493.11 mg, 2.57 mmol, 2 eq) and DMAP (314.25 mg, 2.57 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (200 mL, which was extracted as 100 mL * 2). The combined organic layers were washed with HCl (1 M, 100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, petroleum ether/ethyl acetate = 5/1 to 0/1) to get the compound methyl (2S)-2-[[(2S)-2-[(5-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (600 mg, 1.02 mmol, 79.35% yield, 91% purity) as a white solid. MS (ESI) m/z 535.2/537.2 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl) -2-oxo-ethyl]-7-methoxy-1H-benzimidazole-2-carboxamide

[000880] A mixture of methyl (2S)-2-[[(2S)-2-[(5-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentan oyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (450 mg, 841.07 umol, 1 eq) and NH_3/MeOH (7 M, 15 mL, 124.84 eq) was stirred at

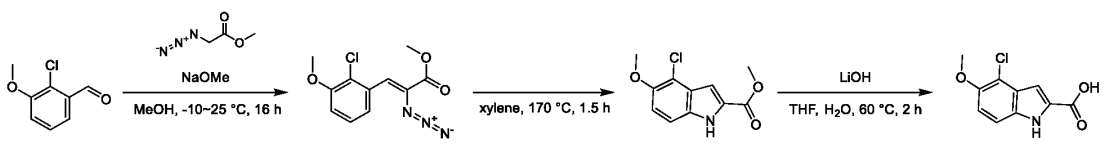
60 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to afford N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-5-chloro-4-methoxy-1H-indole-2-carboxamide (440 mg, 719.20 umol, 85.51% yield, 85% purity) as a white solid. MS (ESI) m/z 520.3 $[M+H]^+$

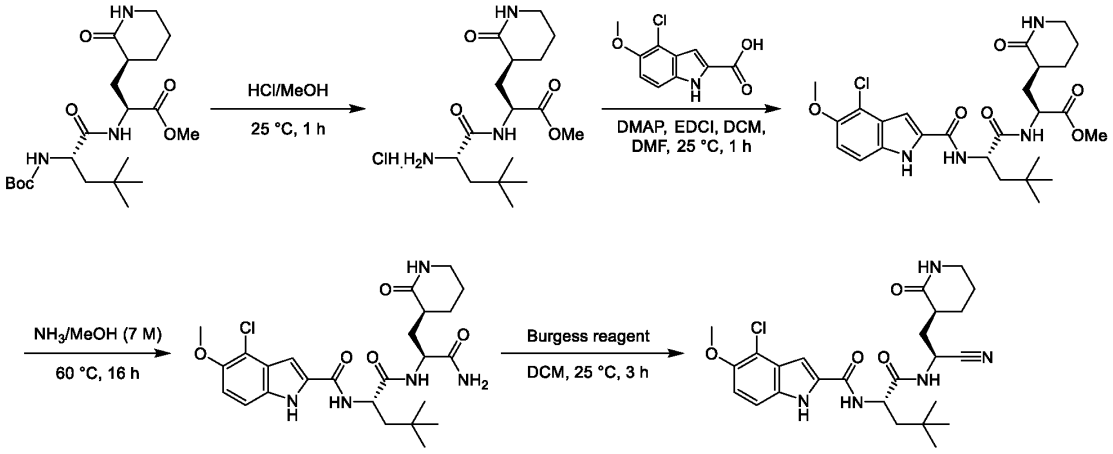
Step 6: 5-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl -butyl]-4-methoxy-1H-indole-2-carboxamide

[000881] To a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-5-chloro-4-methoxy-1H-indole-2-carboxamide (440 mg, 846.12 umol, 1 eq) in DCM (6 mL) was added Burgess reagent (604.92 mg, 2.54 mmol, 3 eq). The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was diluted with H_2O (20 mL) and then extracted with DCM (20 mL * 2). The combined organic layers were concentrated and blow-drying by N_2 to give a residue. The residue was purified by neutral prep-HPLC (column: Kromasil C18 (250 * 50 mm * 10 um); mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 30% - 60%,10 min) to afford 5-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3- dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (220 mg, 430.07 umol, 50.83% yield, 98.134% purity) as a white solid. MS (ESI) m/z 502.2 $[M+H]^+$.

[000882] ^1H NMR (400MHz, DMSO-d_6) δ = 11.85 (br s, 1H), 8.96 (d, J=7.9 Hz, 1H), 8.63 (d, J=8.1 Hz, 1H), 7.67 - 7.38 (m, 2H), 7.24 - 7.05 (m, 2H), 5.16 - 4.92 (m, 1H), 4.63 - 4.42 (m, 1H), 4.11 - 4.02 (m, 3H), 3.14 - 3.00 (m, 2H), 2.36 - 2.17 (m, 2H), 1.88 - 1.62 (m, 5H), 1.59 - 1.29 (m, 2H), 0.94 (s, 9H),

Example 94. Synthesis of viral protease inhibitor compound 808





Step 1: methyl (Z)-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate

[000883] A mixture of 2-chloro-3-methoxy-benzaldehyde (4 g, 23.45 mmol, 1 eq) and NaOMe (2.53 g, 46.90 mmol, 2 eq) with MeOH (20 mL) was cooled to -10 °C, and then a mixture of methyl azide acetate (5.49 g, 46.90 mmol, 2 eq) in MeOH (50 mL) was added dropwise to the solution. The mixture was stirred at 25 °C for 16 h, and a white solid was observed. Upon completion, the reaction mixture was filtered to give a residue compound methyl (Z)-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate (3 g, 10.09 mmol, 43.02% yield, 90% purity) as a white solid.

Step 2: methyl 4-chloro-5-methoxy-1H-indole-2-carboxylate

[000884] A solution of methyl (Z)-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate (1 g, 3.74 mmol, 1 eq) in xylene (20 mL) was warmed to 170 °C, and stirred at 170 °C for 1.5 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with petroleum ether: ethyl acetate = 5: 1 at 25 °C to afford methyl 4-chloro-5-methoxy-1H-indole-2-carboxylate (450 mg, 1.13 mmol, 30.16% yield, 60% purity) as a yellow solid.

Step 3: 4-chloro-5-methoxy-1H-indole-2-carboxylic acid

[000885] To a mixture of methyl 4-chloro-5-methoxy-1H-indole-2-carboxylate (450.00 mg, 1.88 mmol, 1 eq) in THF (10 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (157.59 mg, 3.76 mmol, 2 eq). The mixture was stirred at 60 °C for 2 h. Upon completion, the pH

of the reaction mixture was adjusted pH=3 by addition HCl, and then diluted with H_2O (30 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue compound 4-chloro-5-methoxy-1H-indole-2-carboxylic acid (320 mg, 992.78 umol, 52.87% yield, 70% purity) as a yellow solid.

Step 4: methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl] propanoate

[000886] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]- 3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 1.17 mmol, 1 eq) in HCl/MeOH (4 M, 50.00 mL, 171.01 eq) was stirred at 25 °C for 1 hr. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue compound methyl(2S)-2-[[(2S)-2-amino-4,4- dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (420 mg, 1.15 mmol, 98.69% yield, HCl) as a white solid.

Step 5: methyl (2S)-2-[[(2S)-2-[(4-chloro-5-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl- pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000887] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3- piperidyl]propanoate (420 mg, 1.15 mmol, 1 eq, HCl) and 4-chloro-5-methoxy-1H-indole-2- carboxylic acid (260.43 mg, 1.15 mmol, 1 eq) in DMF (10 mL) and DCM (20 mL) was added EDCI (442.53 mg, 2.31 mmol, 2 eq) and DMAP (282.02 mg, 2.31 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was filtered and then diluted with H_2O (100 mL) and extracted with ethyl acetate 300 mL (150 mL * 2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3/1 to 0/1) to afford methyl (2S)-2-[[(2S)-2-[(4-chloro-5-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentano yl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (350 mg, 588.75 umol, 51.01% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 535.3 $[M+H]^+$

Step 6: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3- dimethyl-butyl]-4-chloro-5-methoxy-1H-indole-2-carboxamide

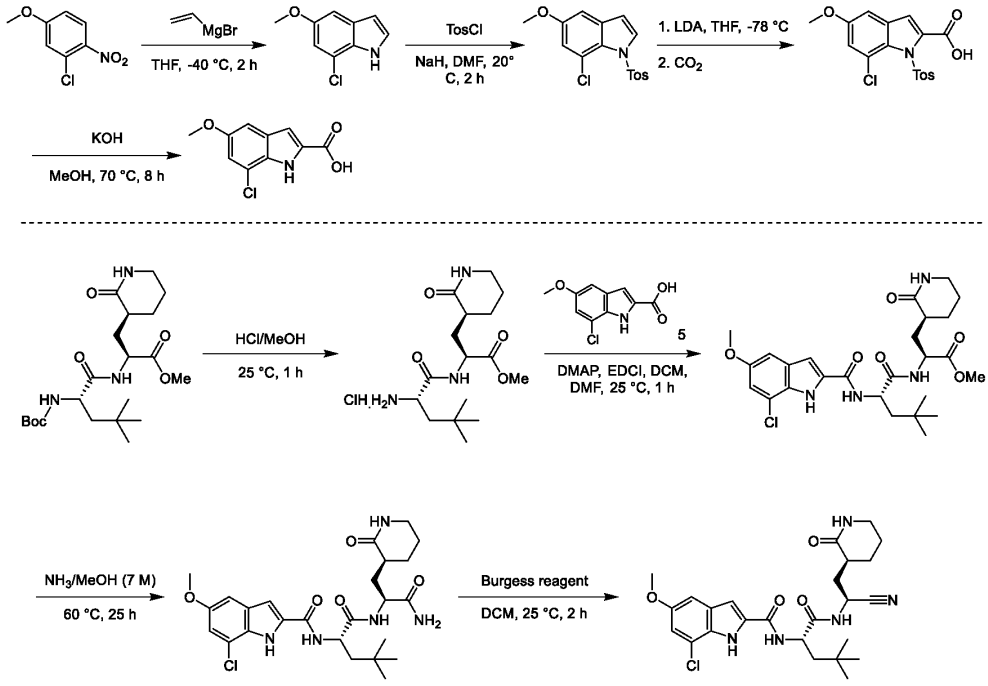
[000888] A mixture of methyl (2S)-2-[[(2S)-2-[(4-chloro-5-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentano yl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (300.00 mg, 560.72 umol, 1 eq) and NH_3/MeOH (7 M, 10 mL, 124 eq) was stirred at 60 °C for 16 h in seal tube. The reaction mixture was concentrated under reduced pressure to give a residue compound N-[(1S)-1-[[(1S)-2-amino-2-oxo-1- [[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-chloro-5-methoxy-1H-indole-2-carboxamide (290 mg, 501.90 umol, 89.51% yield, 90% purity) as a white solid. MS (ESI) *m/z* 520.3 $[M+H]^+$

Step7: 4-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl- butyl]-5-methoxy-1H-indole-2-carboxamide

[000889] To a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl] carbamoyl]-3,3-dimethyl-butyl]-4-chloro-5-methoxy-1H-indole-2-carboxamide (330 mg, 634.59 umol, 1 eq) in DCM (10 mL) was added Burgess reagent (453.69 mg, 1.90 mmol, 3 eq). The mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (40 mL, which was extracted as 20 mL * 2). The combined organic layers were concentrated by blow-drying by N_2 to give a residue. The residue was purified by neutral prep-HPLC(column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 30%-60%,10min) to get the compound 4-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl] ethyl]carbamoyl]-3,3-dimethyl-butyl]-5-methoxy-1H-indole-2-carboxamide (140 mg, 276.09 umol, 43.51% yield, 99% purity) as a white solid. MS (ESI) *m/z* 502.2 $[M+H]^+$.

[000890] ^1H NMR (400MHz, DMSO-*d6*) δ = 11.74 (s, 1H), 8.89 (d, *J*=8.1 Hz, 1H), 8.68 (d, *J*=8.1 Hz, 1H), 7.51 (br s, 1H), 7.41 - 7.25 (m, 2H), 7.13 (d, *J*=8.9 Hz, 1H), 5.12 - 4.96 (m, 1H), 4.52 (dt, *J*=3.8, 8.4 Hz, 1H), 3.91 - 3.76 (m, 3H), 3.14 - 2.95 (m, 2H), 2.37 - 2.13 (m, 2H), 1.90 - 1.29 (m, 7H), 1.01 - 0.81 (m, 9H)

Example 95. Synthesis of viral protease inhibitor compound 810



Step 1: 7-chloro-5-methoxy-1H-indole

[000891] To a solution of 2-chloro-4-methoxy-1-nitro-benzene (4300 mg, 22.92 mmol, 1 *eq*) in THF (70 mL) was added bromo(vinyl)magnesium (1 M, 80.23 mL, 3.5 *eq*) at -40 °C. The solution was stirred for 2 h at -40 °C. Upon completion, the solution was poured into NH_4Cl (200 mL) and concentrated and extracted with ethyl acetate (80 mL * 3) and concentrated to give a crude. The crude was purified by column (SiO_2, petroleum ether:ethyl acetate = 30:1 to 10:1) to give product 7-chloro-5-methoxy-1H-indole (2100 mg, 11.56 mmol, 50.44% yield) as a brown oil. MS (ESI) *m/z* 182.1 $[M+H]^+$.

Step 2: 7-chloro-5-methoxy-1-(p-tolylsulfonyl)indole

[000892] To a solution of 7-chloro-5-methoxy-1H-indole (2100 mg, 11.56 mmol, 1 *eq*) in DMF (25 mL) was added NaH (739.94 mg, 18.50 mmol, 60% purity, 1.6 *eq*) at 0 °C. The solution was stirred for 0.5 h at 20 °C. 4-Methylbenzenesulfonyl chloride (2.09 g, 10.98 mmol, 0.95 *eq*) was added and the solution was stirred for 1.5 h at 20 °C. Upon completion, the solution was diluted with H_2O (60 mL) and extracted with ethyl acetate (60 mL * 3) and then washed with brine (60 mL * 2) and concentrated to give crude. The crude was purified by column (SiO_2, petroleum ether:ethyl acetate = 30:1 to 2:1) to give

7-chloro-5-methoxy-1-(p-tolylsulfonyl)indole (2800 mg, 8.34 mmol, 72.11% yield) as a brown solid. MS (ESI) *m/z* 336.3 $[M+H]^+$

Step 3: 7-chloro-5-methoxy-1-(p-tolylsulfonyl)indole-2-carboxylic acid

[000893] To a solution of 7-chloro-5-methoxy-1-(p-tolylsulfonyl)indole (2800 mg, 8.34 mmol, 1 *eq*) in THF (40 mL) was added LDA (1 M, 16.68 mL, 2 *eq*) at -70 °C and the solution was stirred for 2.5 h at -70 °C. Upon completion, the solution was poured into dry ice quickly and diluted with H_2O (80 mL) and the solution was concentrated and extracted with ethyl acetate (80 mL) to recycle reactant 3. The water layer was acidified to pH=5-6 with HCl (con) and extracted with ethyl acetate (90 mL * 2) and dried over Na_2SO_4 and concentrated to give crude 7-chloro-5-methoxy-1-(p-tolylsulfonyl)indole-2-carboxylic acid (2300 mg, crude) as a brown solid. The crude was used directly for the next step. MS (ESI) *m/z* 380.2 $[M+H]^+$

Step 4: 7-chloro-5-methoxy-1H-indole-2-carboxylic acid

[000894] A solution of 7-chloro-5-methoxy-1-(p-tolylsulfonyl)indole-2-carboxylic acid (2100 mg, 5.53 mmol, 1 *eq*) and KOH (682.51 mg, 12.16 mmol, 14.41 uL, 2.2 *eq*) in MeOH (30 mL) was stirred for 8 h at 70 °C. Upon completion, the solution was concentrated and diluted with H_2O (40 mL) and acidified to pH=5-6 with HCl (1M) and filtered and the cake was collected to give 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (570 mg, crude) as a brown solid. The crude was used directly for the next step. MS (ESI) *m/z* 226.3 $[M+H]^+$

Step 5: methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate;hydrochloride

[000895] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 1.17 mmol, 1 *eq*) in HCl/MeOH (20 mL) was stirred for 1 h at 25 °C. Upon completion, the solution was concentrated to give crude product methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate;hydrochloride (420 mg, crude) as an off-white solid. The crude was used directly for the next step. MS (ESI) *m/z* 364.3 $[M+H]^+$

Step 6: methyl (2S)-2-[[(2S)-2-[(7-chloro-5-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000896] A solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate;hydrochloride (420 mg, 1.15 mmol, 1 *eq*) and DMAP (282.02 mg, 2.31 mmol, 2 *eq*) in DCM (20 mL) and DMF (10 mL) was added 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (299.49 mg, 1.33 mmol, 1.15 *eq*) and EDCI (442.54 mg, 2.31 mmol, 2 *eq*). The reaction was stirred for 1 h at 25 °C. Upon completion, the solution was diluted with H_2O (40 mL), extracted with ethyl acetate (50 mL * 3), and washed with brine (80 mL * 2) and concentrated to give crude product. The crude was purified by column (SiO_2, ethyl acetate:MeOH = 1:0 to 10:1) to give product methyl(2S)-2-[[(2S)-2-[(7-chloro-5-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (370 mg, 691.55 umol, 59.91% yield) as a yellow solid. MS (ESI) *m/z* 535.3 $[M+H]^+$

Step 7: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-chloro-5-methoxy-1H-indole-2-carboxamide

[000897] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-5-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (370 mg, 691.55 umol, 1 *eq*) in NH_3/MeOH (7 M, 16.44 mL, 166.45 *eq*) was stirred for 25 h at 60 °C. Upon completion, the solution was concentrated to give N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-chloro-5-methoxy-1H-indole-2-carboxamide (350 mg, crude) as an off-white solid. The crude was used directly for the next step. MS (ESI) *m/z* 520.3 $[M+H]^+$

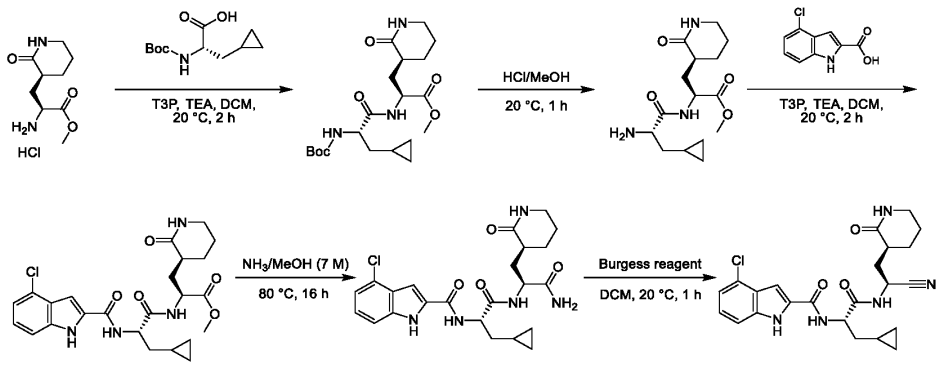
Step 8: 7-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-5-methoxy-1H-indole-2-carboxamide

[000898] A solution of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-chloro-5-methoxy-1H-indole-2-carboxamide (350 mg, 673.05 umol, 1 *eq*) and Burgess reagent (641.57 mg, 2.69 mmol, 4 *eq*) in DCM (20 mL) was stirred for 2 h at 25 °C. Upon completion, the solution was washed with brine (30 mL * 2) and blow dried with N_2 to give crude product. The crude was purified by prep-HPLC (Column: Waters Xbridge Prep OBD C18

150*40mm*10um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min) to afford 7-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-5-methoxy-1H-indole-2-carboxamide (100 mg, 199.20 umol, 29.60% yield) as a white solid. MS (ESI) *m/z* 502.1 $[M+H]^+$.

[000899] ^1H NMR (400MHz, DMSO-d_6) δ = 11.55 (br s, 1H), 9.11 - 8.94 (m, 1H), 8.64 (br d, *J*=8.4 Hz, 1H), 7.52 (br s, 1H), 7.17 - 7.08 (m, 2H), 6.98 (d, *J*=2.0 Hz, 1H), 5.27 - 4.92 (m, 1H), 4.69 - 4.37 (m, 1H), 3.76 (s, 3H), 3.05 (br s, 2H), 2.30 - 2.16 (m, 2H), 2.06 (s, 1H), 1.83 - 1.66 (m, 4H), 1.57 - 1.32 (m, 2H),

Example 96. Synthesis of viral protease inhibitor compound 812



Step 1: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000900] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 4.22 mmol, 1 *eq*, HCl) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (968.64 mg, 4.22 mmol, 1 *eq*), TEA (1.28 g, 12.67 mmol, 1.76 mL, 3 *eq*) in DCM (15 mL) was added T3P (8.07 g, 12.67 mmol, 7.54 mL, 50% purity, 3 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (20 mL) at 0 °C, the combined organic layers were washed with DCM (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=2/1 to 0/1) to give methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.08 g, 2.05 mmol, 48.46% yield, 78% purity) as a yellow oil. MS (ESI) *m/z* 413.2 $[M+H]^+$.

Step 2: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000901] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.04 g, 2.53 mmol, 1 *eq*) in HCl/MeOH (15 mL) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (879 mg, crude, HCl) as a yellow oil. MS (ESI) *m/z* 313.2 $[M+H]^+$

Step 3 : *methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate*

[000902] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (879 mg, 2.82 mmol, 1 *eq*) and 4-chloro-1H-indole-2-carboxylic acid (552.18 mg, 2.82 mmol, 1 *eq*) TEA (856.96 mg, 8.47 mmol, 1.18 mL, 3 *eq*) in DCM (10 mL) was added T3P (5.39 g, 8.47 mmol, 5.04 mL, 50% purity, 3 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (20 mL) at 0 °C, the combined organic layers were washed with DCM (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=2/1 to 0/1) to afford methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (636 mg, 1.04 mmol, 36.86% yield, 80% purity) as a yellow solid. MS (ESI) *m/z* 489.2 $[M+H]^+$

Step 4: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-indole-2-carboxamide

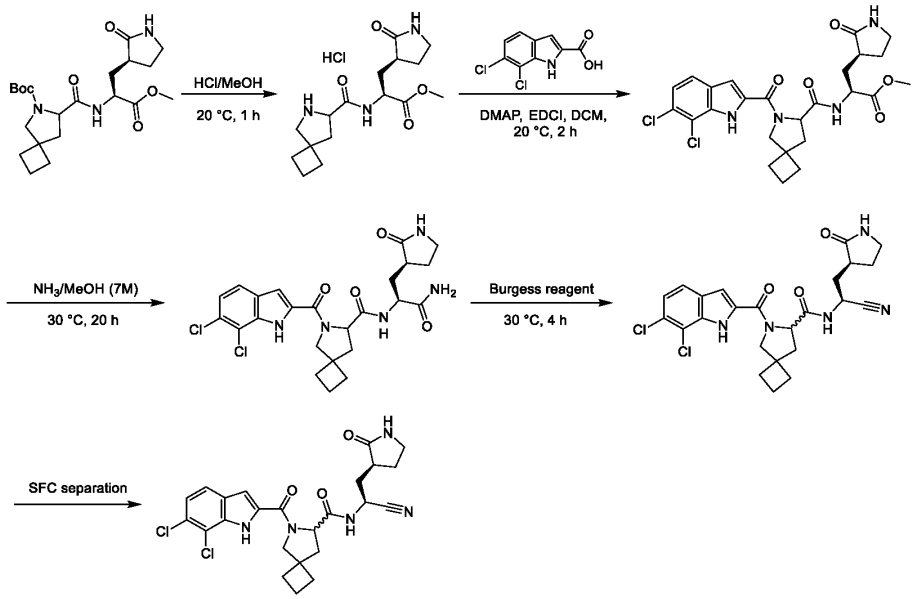
[000903] A solution of methyl (2S)-2-[[(2S)-2-[(4-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (621 mg, 1.27 mmol, 1 *eq*) in NH_3/MeOH (7 M, 5 mL, 27.56 *eq*) was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-indole-2-carboxamide (460 mg, crude) as a yellow solid. MS (ESI) *m/z* 474.2 $[M+H]^+$.

Step 5: 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000904] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-indole-2-carboxamide (440 mg, 928.37 umol, 1 *eq*) in DCM (8 mL) was added Burgess reagent (663.70 mg, 2.79 mmol, 3 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (105.2 mg, 229.35 umol, 24.70% yield, 99.4% purity) as a white solid. MS (ESI) *m/z* 456.2 $[M+H]^+$.

[000905] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.95 (s, 1H), 8.92 (d, *J* = 8.4 Hz, 1H), 8.81 - 8.70 (m, 1H), 7.55 - 7.49 (m, 1H), 7.44 - 7.37 (m, 2H), 7.24 - 7.07 (m, 2H), 5.14 - 5.00 (m, 1H), 4.54 - 4.40 (m, 1H), 3.18 - 2.99 (m, 2H), 2.31 - 2.21 (m, 2H), 1.93 - 1.66 (m, 4H), 1.61 - 1.34 (m, 3H), 0.89 - 0.76 (m, 1H), 0.52 - 0.33 (m, 2H), 0.24 - 0.04 (m, 2H)

Example 97. Synthesis of viral protease inhibitor compound 814



Step 1: (2S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-(6-azaspiro[3.4]octane-7-carboxamido)propanoate

[000906] A solution of tert-butyl 7-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl) carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate (1.4 g, 3.31 mmol, 1 eq) in HCl/MeOH (4 M, 14 mL) was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was concentrated in vacuum to obtain (2S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-(6-azaspiro[3.4] octane-7-carboxamido) propanoate (1.29 g, crude) as a light yellow solid.

Step 2: (2S)-methyl2-(6-(6,7-dichloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000907] To a solution of (2S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-(6-azaspiro[3.4] octane-7-carboxamido) propanoate (1.14 g, 2.22 mmol, 70% purity, 1 *eq*, HCl) in DCM (25 mL) was added 6,7-dichloro-1H-indole-2-carboxylic acid (612.19 mg, 2.66 mmol, 1.2 *eq*) and DMAP (541.85 mg, 4.44 mmol, 2 *eq*) and EDCI (850.23 mg, 4.44 mmol, 2 *eq*). The mixture was stirred at 20 °C for 2 h. Upon the reaction completion, the residue was poured into water (60 mL) and was extracted with DCM (20 mL * 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1, Rf = 0.35) to obtained (2S)-methyl 2-(6-(6,7-dichloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7- carboxamido)-3-((S)-2-oxopyrrolidin-3-yl) propanoate (800 mg, 1.48 mmol, 66.70% yield, 99% purity) as a light yellow solid. MS (ESI) m/z 535.2 $[M+H]^+$

Step 3: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-6-(6,7-dichloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000908] A solution of (2S)-methyl 2-(6-(6,7-dichloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7- carboxamido)-3-((S)-2-oxopyrrolidin-3-yl) propanoate (270 mg, 504.28 umol, 1 *eq*) in NH_3/MeOH (6 mL, 7 M) was stirred at 30 °C for 20 h. Upon the reaction completement, the mixture was concentrated in vacuum to obtained N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl) propan-2-yl)-6-(6,7-dichloro-1H-indole -2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (800 mg, crude) as a light yellow solid. MS (ESI) m/z 520.2 $[M+H]^+$

Step 4: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-6-(6,7-dichloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000909] To a solution of N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl) propan-2-yl)-6-(6,7-dichloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (800 mg, 1.54 mmol, 1 *eq*) in DCM (15 mL) was added Burgess reagent (1.10 g, 4.61 mmol, 3 *eq*), and the mixture was stirred at 30 °C for 4 h. Upon the reaction completion, the mixture was quenched by H_2O (2 mL) and dried by blowing N_2 and was purified by prep-HPLC (column: Waters Xbridge C18 150 * 50 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 35%-65%, 10 min) to obtained N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-6-(6,7-dichloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (380 mg, 756.38 umol, 49.20% yield) as a white solid. MS (ESI) m/z 502.2 $[M+H]^+$.

Step 5: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-6-(6,7-dichloro-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

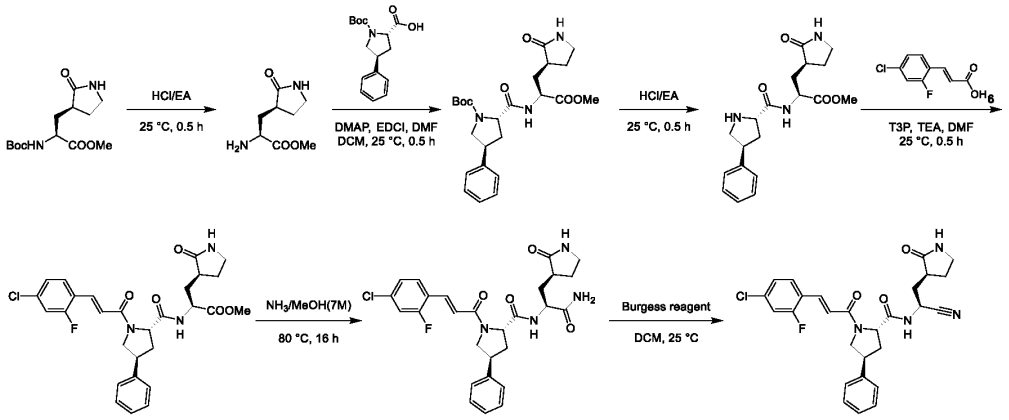
[000910] The N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl) ethyl) -6-(6,7-dichloro-1H-indole-2-carbonyl) -6-azaspiro[3.4]octane-7-carboxamide was separated by SFC (column: DAICEL CHIRALPAK AS(250mm * 30mm, 10um); mobile phase: [0.1% NH_3H_2O MEOH]; B%: 45%-45%, 15min) to obtained N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl) ethyl) -6-(6,7-dichloro-1H-indole-2-carbonyl) -6-azaspiro[3.4]octane-7-carboxamide (Isomer 1: 110 mg, 218.95 umol, 28.95% yield, 100% purity) as a white solid. MS (ESI) m/z 502.1 $[M+H]^+$

[000911] ^1H NMR (400 MHz, MeOD-d_4) δ ppm 7.62 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.17 (s, 1H), 5.01 (dd, J = 5.8, 10.3 Hz, 1H), 4.58 (t, J = 7.6 Hz, 1H), 4.08 - 3.80 (m, 2H), 3.15 - 2.58 (m, 1H), 2.55 - 2.15 (m, 5H), 2.11 - 1.74 (m, 9H).

[000912] To obtain N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl) -6-(6,7-dichloro-1H-indole-2- carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (Isomer 2: 85 mg, 169.19 umol, 22.37% yield, 100% purity) after repurification by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 30%-65%, 10 min) as a white solid. MS (ESI) m/z 502.1 $[M+H]^+$

[000913] ^1H NMR (400 MHz, MeOD-d_4) δ ppm 7.61 (d, J = 8.6 Hz, 1H), 7.24 - 7.15 (m, 1H), 7.13 (s, 1H), 5.09 - 4.90 (m, 1H), 4.78 - 4.51 (m, 1H), 4.06 - 3.72 (m, 2H), 2.83 - 2.63 (m, 1H), 2.61 - 2.28 (m, 3H), 2.22 - 1.76 (m, 10 H), 1.72 - 1.40 (m, 1H).

Example 98. Synthesis of viral protease inhibitor compound 171



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000914] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.55 g, 1.92 mmol, 1 *eq*) and HCl/EtOAc (4 M, 10 mL, 20.82 *eq*) was stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate (0.35 g, crude) as a yellow oil.

Step 2: (2S,4S)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate

[000915] A mixture of (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate (0.15 g, 805.55 umol, 1 *eq*), (2S,4S)-1-tert-butoxycarbonyl-4-phenyl-pyrrolidine-2-carboxylic acid (234.69 mg, 805.55 umol, 1 *eq*), DMAP (196.83 mg, 1.61 mmol, 2 *eq*), EDCI (308.85 mg, 1.61 mmol, 2 *eq*) in DMF (1 mL) and DCM (2 mL) was stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 2:1 to 0:1) to give (2S,4S)-tert-butyl 2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-phenyl-pyrrolidine-1-carboxylate (0.25 g, 500.51 umol, 62.13% yield, 92% purity) as a colorless oil. MS (ESI) *m/z* 460.1 $[M+H]^+$.

Step 3: (S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-((2S,4S)-4-phenylpyrrolidine-2-carboxamido)propanoate

[000916] A mixture of tert-butyl (2S,4S)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-phenyl-pyrrolidine-1-carboxylate (0.25 g, 544.03 umol, 1 *eq*) and HCl/EtOAc (4 M, 10 mL, 73.53 *eq*) was stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(2S,4S)-4-phenylpyrrolidine-2-carbonyl]amino]propanoate (0.2 g, crude) as a yellow oil. MS (ESI) *m/z* 360.1 $[M+H]^+$.

Step 4: (S)-methyl 2-((2S,4S)-1-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-4-phenylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000917] A mixture of methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(2S,4S)-4-phenylpyrrolidine-2-carbonyl]amino]propanoate (0.17 g, 472.99 umol, 1 *eq*), (E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoic acid (94.88 mg, 472.99 umol, 1 *eq*), T3P (451.48 mg, 709.48 umol, 421.95 uL, 50% purity, 1.5 *eq*), TEA (143.58 mg, 1.42 mmol, 197.50 uL, 3 *eq*) in DMF (4 mL) was degassed and stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 2:1 to 0:1) to give methyl (2S)-2-[[(2S,4S)-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.11 g, 162.36 umol, 34.33% yield, 80% purity) as a white solid. MS (ESI) *m/z* 542.1 $[M+H]^+$.

Step 5: (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-4-phenylpyrrolidine-2-carboxamide

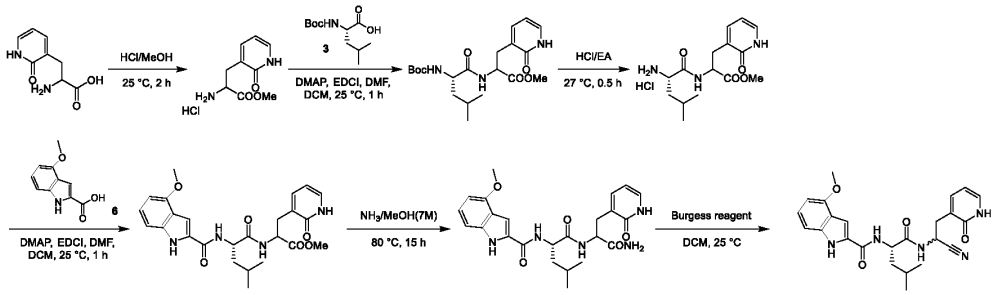
[000918] A mixture of methyl (2S)-2-[[(2S,4S)-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.1 g, 184.50 umol, 1 *eq*) in NH_3/MeOH (3 mL, 7 M) was stirred at 80 °C for 16 h in the sealed tube. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-4-phenyl-pyrrolidine-2-carboxamide (0.09 g, crude) as a yellow oil. MS (ESI) *m/z* 527.0 $[M+H]^+$.

Step 6: (2S,4S)-1-((E)-3-(4-chloro-2-fluorophenyl)acryloyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-4-phenylpyrrolidine-2-carboxamide

[000919] To a solution of (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-4-phenyl-pyrrolidine-2-carboxamide (0.09 g, 170.78 umol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (203.50 mg, 853.91 umol, 5 *eq*), and then the solution was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min) to give (2S,4S)-1-[(E)-3-(4-chloro-2-fluoro-phenyl)prop-2-enoyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-phenyl-pyrrolidine-2-carboxamide (29.73 mg, 56.89 umol, 33.31% yield, 97.4% purity) as a white solid. MS (ESI) *m/z* 509.1 $[M+H]^+$.

[000920] ^1H NMR (400 MHz, DMSO-d_6) δ = 9.17 - 8.86 (m, 1H), 8.07 - 7.75 (m, 1H), 7.75 - 7.65 (m, 1H), 7.62 - 7.49 (m, 2H), 7.48 - 7.30 (m, 5H), 7.26 (tt, *J* = 3.0, 5.6 Hz, 1H), 7.22 - 6.73 (m, 1H), 5.09 - 4.83 (m, 1H), 4.69 - 4.47 (m, 1H), 4.40 - 4.01 (m, 1H), 3.77 - 3.50 (m, 3H), 3.19 - 3.04 (m, 2H), 2.44 - 2.31 (m, 2H), 2.22 - 2.09 (m, 2H), 1.88 - 1.59 (m, 2H).

Example 99. Synthesis of viral protease inhibitor compound 253



Step 1: methyl 2-amino-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate

[000921] A mixture of 2-amino-3-(2-oxo-1H-pyridin-3-yl)propanoic acid (500 mg, 2.74 mmol, 1 *eq*) and HCl/MeOH (4 M, 30 mL, 43.72 *eq*) was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a product methyl 2-amino-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (650 mg, crude, HCl) as a yellow oil and used directly for next step. MS (ESI) *m/z* 197.0 $[M+H]^+$

Step 2: methyl-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate

[000922] A mixture of methyl 2-amino-3-(2-oxo-1H-pyridin-3-yl)propanoate (650 mg, 2.79 mmol, 1 *eq*, HCl), (2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoic acid (646.16 mg, 2.79 mmol, 1 *eq*), EDCI (1.07 g, 5.59 mmol, 2 *eq*), DMAP (682.62 mg, 5.59 mmol, 2 *eq*), DMF (2 mL) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 0/1) to get the product methyl-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (900 mg, 1.89 mmol, 67.68% yield, 86.02% purity), as white solid. MS (ESI) *m/z* 410.1 $[M+H]^+$

Step 3: methyl 2-((S)-2-amino-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate

[000923] A mixture of methyl-2-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (200 mg, 488.43 umol, 1 *eq*) and HCl/EtOAc (4 M, 30 mL) was stirred at 27 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give methyl 2-((S)-2-amino-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (170 mg, crude, HCl) as a white solid and used directly for next step.

Step 4: methyl 2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate

[000924] A mixture of methyl 2-((S)-2-amino-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (170 mg, 491.58 umol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (93.98 mg, 491.58 umol, 1 *eq*), EDCI (188.47 mg, 983.17 umol, 2 *eq*), DMAP (120.11 mg, 983.17 umol, 2 *eq*), DMF (2 mL) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 0/1) to afford methyl 2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-

methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (130 mg, 269.41 umol, 54.81% yield) as white solid. MS (ESI) *m/z* 483.1 $[M+H]^+$

Step 5: N-((2S)-1-((1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

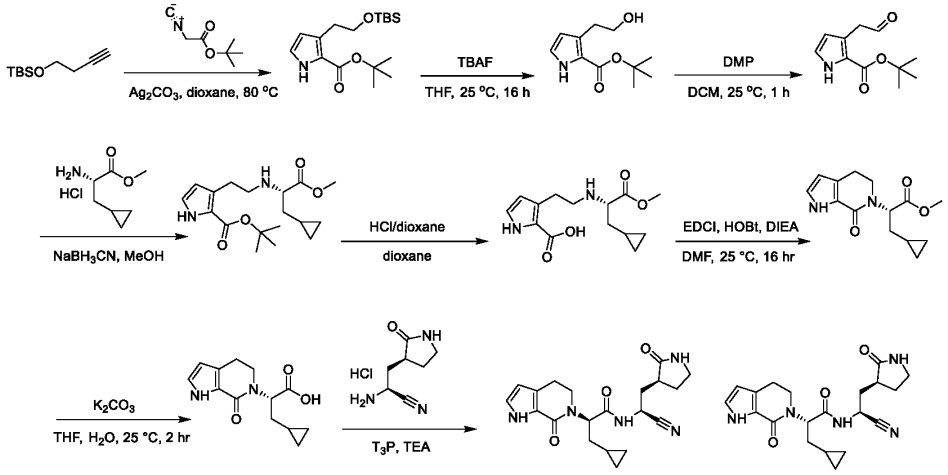
[000925] A mixture of methyl 2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-(2-oxo-1,2-dihydropyridin-3-yl)propanoate (190 mg, 393.76 umol, 1 *eq*), NH_3/MeOH (7 M, 10 mL) was stirred at 80 °C for 15 h. The reaction mixture was concentrated under reduced pressure to give a residue N-((2S)-1-((1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (190 mg, crude) as a yellow solid. MS (ESI) *m/z* 468.2 $[M+H]^+$

Step 6: N-((2S)-1-((1-cyano-2-(2-oxo-1,2-dihydropyridin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000926] A mixture of N-((2S)-1-((1-amino-1-oxo-3-(2-oxo-1,2-dihydropyridin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (180 mg, 385.01 umol, 1 *eq*), Burgess reagent (917.53 mg, 3.85 mmol, 10 *eq*) and DCM (30 mL) was stirred at 25 °C for 8 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 25%-45%,8min) to get the product N-((2S)-1-((1-cyano-2-(2-oxo-1,2-dihydropyridin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (24 mg, 52.18 umol, 13.55% yield, 97.73% purity), as yellow solid. MS (ESI) *m/z* 450.2 $[M+H]^+$.

[000927] ^1H NMR (400MHz, DMSO-d_6) δ = 11.90-11.40 (m, 2H), 9.08 - 8.85 (m, 1H), 8.55 - 8.35 (m, 1H), 7.51 - 7.26 (m, 3H), 7.16 - 7.05 (m, 1H), 7.04 - 6.94 (m, 1H), 6.51 (d, J=7.5 Hz, 1H), 6.15 (t, J=6.6 Hz, 1H), 5.19 - 5.01 (m, 1H), 4.55 - 4.33 (m, 1H), 3.89 (s, 3H), 3.02 - 2.78 (m, 2H), 1.75 - 1.33 (m, 3H), 0.98 - 0.72 (m, 6H).

Example 100. Synthesis of viral protease inhibitor compound 267 & 267A



Step 1: tert-Butyl 3-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-1H-pyrrole-2-carboxylate

[000928] To a solution of tert-butyl-but-3-ynoxy-dimethyl-silane (5.00 g, 27.10 mmol, 1.5 *eq*) and Ag_2CO_3 (498 mg, 1.81 mmol, 0.1 *eq*) in dioxane (8 mL) was added *tert*-butyl 2-isocyanoacetate (2.55 g, 18.06 mmol, 2.63 mL, 1 *eq*). Then the mixture was stirred at 80 °C for 1 hr. TLC (petroleum ether/ethyl acetate = 10/1, UV) showed that the starting material was consumed completely and new spots formed. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~10% ethyl acetate/petroleum ether gradient @ 30 mL/min). tert-butyl 3-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-1*H*-pyrrole-2-carboxylate (2.5 g, 42.5% yield) was obtained as a white solid.

Step 2: tert-Butyl 3-(2-hydroxyethyl)-1H-pyrrole-2-carboxylate

[000929] To a solution of *tert*-butyl 3-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-1*H*-pyrrole-2-carboxylate (2.5 g, 7.68 mmol, 1 *eq*) in THF (20 mL) was added TBAF (1 M, 15.3 mL, 2 *eq*) at 0 °C, and then the mixture was stirred at 25 °C for 16 hr. TLC (petroleum ether/ethyl acetate = 5/1, UV) showed that the starting material was consumed completely and new spot formed. The reaction mixture was concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @ 30 mL/min). *tert*-butyl 3-(2-hydroxyethyl)-1*H*-pyrrole-2-carboxylate (1.3 g, 80.1% yield) was obtained as colorless oil.

Step 3: tert-Butyl 3-(2-oxoethyl)-1H-pyrrole-2-carboxylate

[000930] To a solution of *tert*-butyl 3-(2-hydroxyethyl)-1*H*-pyrrole-2-carboxylate (1.15 g, 5.44 mmol, 1 *eq*) in DCM (20 mL) was added DMP (3.23 g, 7.62 mmol, 1.4 *eq*) and the mixture was stirred at 25 °C for 1 hr. LCMS showed that the starting material was remained and ~60% of the desired product was detected. TLC (petroleum ether/ethyl acetate = 5/1, UV) showed that the starting material was consumed completely and new spot formed. The reaction mixture was filtered and the filtrated was concentrated in vacuum. The residue was diluted with ethyl acetate (50 mL), washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~20% ethyl acetate/petroleum ether gradient @ 30 mL/min). *tert*-butyl 3-(2-oxoethyl)-1*H*-pyrrole-2-carboxylate (1.5 g, 65.8% yield) was obtained as colorless oil.

[000931] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 - 9.60 (m, 1H), 9.48 (br s, 1H), 6.91 (t, J = 2.76 Hz, 1H), 6.16 (t, J = 2.51 Hz, 1H), 3.82 (d, J = 1.76 Hz, 2H,), 1.56 (s, 9H).

Step 4: tert-Butyl 3-[2-[[(1S)-1-(cyclopropylmethyl)-2-methoxy-2-oxo-ethyl]amino]ethyl]-1H-pyrrole-2-carboxylate

[000932] A solution of *tert*-butyl 3-(2-oxoethyl)-1*H*-pyrrole-2-carboxylate (1.5 g, 7.17 mmol, 1 *eq*) and methyl (2*S*)-2-amino-3-cyclopropyl-propanoate (1.29 g, 7.17 mmol, 1 *eq*, HCl) in MeOH (20 mL) was stirred at 25 °C for 0.5 hr. Then $NaBH_3CN$ (900.9 mg, 14.34 mmol, 2 *eq*) was added to the mixture and the result solution was stirred at 25 °C for 16 hr. LCMS showed that the starting material was consumed completely and 40% of the desired product was detected. TLC (petroleum ether/ethyl acetate = 5/1, UV) showed that the starting material was consumed completely and new spots formed. The reaction mixture was quenched with H_2O (10 mL), extracted with ethyl acetate (15 mL×3). The combined organic phase was washed with H_2O (10 ml) and brine (10 mL×2), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~20% ethyl acetate/petroleum ether gradient @ 30 mL/min). *tert*-butyl 3-[2-[[(1*S*)-1-(cyclopropylmethyl)-2-methoxy-2-oxo-ethyl]amino]ethyl]-1*H*-pyrrole-2-carboxylate (0.6 g, 24.8% yield) was obtained as colorless oil.

[000933] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (br s, 1H), 6.91 - 6.65 (m, 1H), 6.15 (t, *J* = 2.56 Hz, 1H), 3.71 (s, 3H), 3.40 (t, *J* = 6.69 Hz, 1H), 2.99 - 2.92 (m, 2H), 2.82 - 2.90 (m, 1H), 2.78 - 2.69 (m, 1H), 1.68 - 1.63 (m, 1H), 1.57 (s, 9H), 1.50 - 1.42 (m, 1H), 0.76 - 0.66 (m, 1H), 0.48 - 0.36 (m, 2H), 0.11 - 0.01 (m, 2H).

Step 5: 3-[2-[[(1S)-1-(Cyclopropylmethyl)-2-methoxy-2-oxo-ethyl]amino]ethyl]-1H-pyrrole-2-carboxylic acid

[000934] To a solution of *tert*-butyl 3-[2-[[(1*S*)-1-(cyclopropylmethyl)-2-methoxy-2-oxo-ethyl]amino]ethyl]-1*H*-pyrrole-2-carboxylate (0.2 g, 0.59 mmol, 1 *eq*) in dioxane (1 mL) was added HCl/dioxane (4 M, 1.49 mL, 10 *eq*) and the mixture was stirred at 25 °C for 16 hr. LCMS showed that the starting material was consumed completely and 88% of the desired product was detected. The reaction mixture was concentrated in vacuum. The crude product was used for the next step directly. 3-[2-[[(1*S*)-1-(cyclopropylmethyl)-2-methoxy-2-oxo-ethyl]amino]ethyl]-1*H*-pyrrole-2-carboxylic acid (0.15 g, 90% yield) was obtained as black brown oil.

Step 6: Methyl (2S)-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1H-pyrrolo[2,3-c]pyridin-6-yl)propanoate

[000935] To a solution of 3-[2-[[(1*S*)-1-(cyclopropylmethyl)-2-methoxy-2-oxo-ethyl]amino]ethyl]-1*H*-pyrrole-2-carboxylic acid (150 mg, 0.53 mmol, 1 *eq*) in DMF (1 mL) were added HOBt (108.4 mg, 0.802 mmol, 1.5 *eq*), DIEA (207.4 mg, 1.61 mmol, 0.28 mL, 3 *eq*) and EDCI (153.8 mg, 0.80 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 16 hr. LCMS showed that the starting material was consumed completely and 45% of the desired product was detected. TLC (petroleum ether/ethyl acetate = 2/1, UV) showed that the starting material was consumed completely and new spots formed. The reaction mixture was quenched with H_2O (20 mL), extracted with ethyl acetate (20 mL*3). The combined organic phase was washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 30 mL/min). methyl (2*S*)-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanoate (85 mg, 58.1% yield) was obtained as colorless oil.

[000936] LCMS: Rt = 0.773 min; for $C_{14}H_{18}N_2O_3$ MS Calcd. 262.13; MS Found 263.0 [$M+H^+$].

[000937] ^1H NMR (400 MHz, CD_3OD) δ 6.97 - 6.85 (m, 1H), 6.04 (d, *J* = 2.26 Hz, 1H,), 5.09 (dd, *J* = 10.26, 5.27 Hz, 1H), 3.71 (s, 3H), 3.67 - 3.58 (m, 2 H), 2.93 - 2.74 (m, 2H), 2.02 - 1.87 (m, 1H), 1.81 - 1.70 (m, 1H), 0.83 - 0.68 (m, 1H), 0.56 - 0.39 (m, 2H), 0.22 - 0.07 (m, 2H).

Step 7: (2S)-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1H-pyrrolo[2,3-c]pyridin-6-yl)propanoic acid

[000938] To a solution of methyl (2*S*)-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanoate (60 mg, 0.228 mmol, 1 *eq*) in MeOH (2 mL) was added K_2CO_3 (94.8 mg, 0.686 mmol, 3 *eq*) in H_2O (1 mL) and the mixture was stirred at 25 °C for 16 hr. LCMS showed that the starting material was consumed completely and 100% of the desired product was detected. The reaction mixture was diluted with H_2O (5 mL), adjusted pH = 3 with 0.5 M aq.HCl and extracted with ethyl acetate (15 mL*3). The combined organic phase was washed with H_2O (5 mL), brine (5 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was used for the next step directly. (2*S*)-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanoic acid was obtained as a white solid.

[000939] LCMS: Rt = 0.706 min; for $C_{13}H_{16}N_2O_3$ MS Calcd. 248.12; MS Found 248.9 [$M+H^+$].

[000940] 267A: (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanamide

[000941] 267: (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanamide

[000942] To a solution of (2*S*)-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanoic acid (40 mg, 0.16 mmol, 1 *eq*) and (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanenitrile (30.5 mg, 0.16 mmol, 1 *eq*, HCl) in DMF (1 mL) were added TEA (32.6 mg, 0.32 mmol, 44 uL, 2 *eq*) and T_3P (153.7 mg, 0.241 mmol, 0.14 mL, 50% purity, 1.5 *eq*) at 25 °C, and the mixture was stirred at 25 °C for 1 hr. LCMS showed

that the starting material was consumed completely and 86% of the desired product was detected. The reaction mixture was concentrated in vacuum. The residue was checked by HPLC and purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40mm*3um; mobile phase: [water (0.05%NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 20%-50%, 7.8 min). (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanamide (22 mg, 35.6% yield) was obtained as a white solid.

[000943] The crude product was purified by chiral SFC (column: DAICEL CHIRALPAK AS(250mm*30mm,10um); mobile phase: [0.1%NH_3H_2O ETOH]; B%: 30%-30%,min). (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanamide (2.0 mg, 8.7% yield) was obtained as a white solid and (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanamide (15.1 mg, 68.2% yield) was obtained as a white solid.

267A:

[000944] LCMS: Rt = 0.746 min; for $C_{20}H_{25}N_5O_3$ MS Calcd. 383.20; MS Found 384.1 [$M+H^+$].

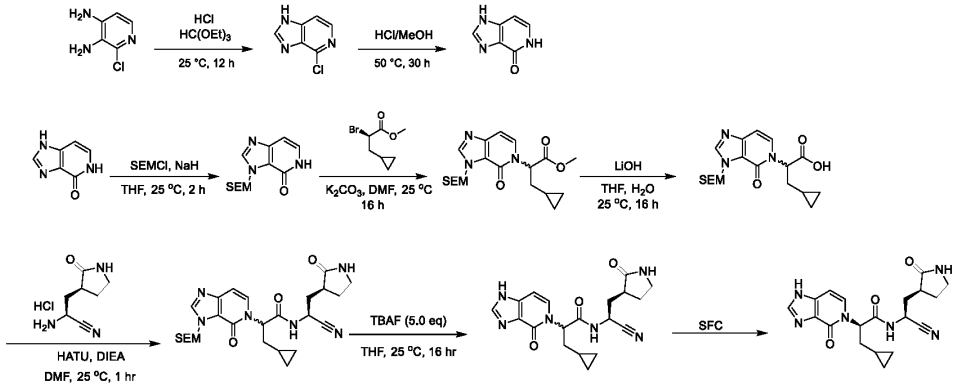
[000945] ^1H NMR (400 MHz, CD_3OD) δ 6.91 (d, *J* = 2.50 Hz, 1H). 6.04 (d, *J* = 2.38 Hz, 1H), 5.15 (dd, *J* = 8.44, 6.94 Hz, 1H),5.04 (br d, *J* = 6.75 Hz, 1H), 3.66 - 3.55 (m, 2H), 3.33 (br s, 2H), 2.88 - 2.76 (m, 2H), 2.55 - 2.42 (m, 1H), 2.39 - 2.23 (m, 2H), 1.96 - 1.83 (m, 2H), 1.82 - 1.74 (m, 2H), 0.70 (br s, 1H), 0.46 (t, *J* = 7.88 Hz, 2H), 0.15 (d, *J* = 4.38 Hz, 2H).

267:

[000946] LCMS: Rt = 0.751 min; for $C_{20}H_{25}N_5O_3$ MS Calcd. 383.20; MS Found 384.1 [$M+H^+$].

[000947] ^1H NMR (400 MHz, CD_3OD) δ 6.90 (d, *J* = 2.38 Hz, 1H), 6.03 (d, *J* = 2.25 Hz, 1H), 5.02 (dd, *J* = 10.13, 6.63 Hz, 2H), 3.66 (tq, *J* = 13.12, 6.34 Hz, 2H), 3.30 - 3.18 (m, 2H), 2.80 (br t, *J* = 6.19 Hz, 2H), 2.59 - 2.44 (m, 1H), 2.37 - 2.21 (m, 2H), 1.97 - 1.69 (m, 4H), 0.78 - 0.67 (m, 1H), 0.60 - 0.42 (m, 2H), 0.17 (d, *J* = 4.50 Hz, 2H).

Example 101. Synthesis of viral protease inhibitor compound 481 & 269A



Step 1: 4-chloro-1H-imidazo[4,5-c]pyridine

[000948] A mixture of 2-chloropyridine-3,4-diamine (3 g, 20.90 mmol, 1 eq) and HCl (2.06 g, 20.90 mmol, 2.0 mL, 37% purity, 1 eq) in diethoxymethoxyethane (30.9 g, 208.95 mmol, 34.7 mL, 10 eq) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 12 hr under N_2 atmosphere. The precipitate formed was filtered, washed with PE. No purification. Compound 4-chloro-1H-imidazo[4,5-c]pyridine (3 g, 93.4% yield) was obtained as a white solid.

Step 2: 1,5-dihydroimidazo[4,5-c]pyridin-4-one

[000949] To a solution of 4-chloro-1H-imidazo[4,5-c]pyridine (3 g, 19.54 mmol, 1 eq) and HCl (1.9 g, 19.54 mmol, 1.8 mL, 37% purity, 1 eq) in MeOH (10 mL). The mixture was stirred at 50 °C for 30 hr. The reaction mixture was concentrated under reduced pressure to remove HCl/MeOH. The crude product was triturated with PE at 25 °C for 150 min. Compound 1,5-dihydroimidazo[4,5-c]pyridin-4-one (2.5 g, crude) was obtained as yellow solid.

Step 3: 3-(2-trimethylsilylethoxymethyl)-5H-imidazo[4,5-c]pyridin-4-one

[000950] To a solution of 1,5-dihydroimidazo[4,5-c]pyridin-4-one (2.5 g, 18.50 mmol, 1 eq) and SEM-Cl (3.0 g, 18.50 mmol, 3.2 mL, 1 eq) in THF (1 mL) was added NaH (2.2 g, 55.50 mmol, 60% purity, 3 eq). The mixture was stirred at 25 °C for 2 hr. TLC (petroleum ether/ethyl acetate = 0:1, UV 254) indicated starting material was remained and new spots formed. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL *3). The combined organic layers were washed with brine (30

mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 100% petroleum ether/ethyl acetate @ 35 mL/min). Compound 3-(2-trimethylsilylethoxymethyl)-5H-imidazo[4,5-c]pyridin-4-one (1.8 g, 32.2% yield, 88% purity) was obtained as yellow solid.

Step 4: Methyl 3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propanoate

[000951] To a solution of 3-(2-trimethylsilylethoxymethyl)-5H-imidazo[4,5-c]pyridin-4-one (1.5 g, 5.65 mmol, 1 eq) and methyl (2*R*)-2-bromo-3-cyclopropyl-propanoate (1.1 g, 5.65 mmol, 1 eq) in DMF (4 mL) was added K_2CO_3 (1.5 g, 11.30 mmol, 2 eq). The mixture was stirred at 25 °C for 16 hr. TLC (petroleum ether/ethyl acetate = 3:1, UV 254) indicated starting material was remained and new spots formed. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL *3). The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 40% petroleum ether/ethyl acetate @ 35 mL/min). Compound methyl 3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propanoate (865 mg, 36.7% yield, 94% purity) was obtained as a white solid.

Step 5: 3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propanoic acid

[000952] To a solution of methyl 3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propanoate (865 mg, 2.21 mmol, 1 eq) in H_2O (1 mL) and THF (1 mL) was added $LiOH.H_2O$ (185.4 mg, 4.42 mmol, 2 eq). The mixture was stirred at 25 °C for 16 hr. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H_2O (2 mL) and added HCl (2 mL, 2 N). The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL *3). The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with PE at 25 °C for 60 min. Compound

3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propanoic acid (746 mg, 86.7% yield, 97% purity) was obtained as a white solid.

[000953] 481 (N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propenamide): A mixture of (2*S*)-3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propanoic acid (600 mg, 1.59 mmol, 1 eq), (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanenitrile (301.4 mg, 1.59 mmol, 1 eq, HCl), HATU (604.3 mg, 1.59 mmol, 1 eq), DIPEA (410.8 mg, 3.18 mmol, 0.55 mL, 2 eq) in DCM (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. TLC (petroleum ether/ethyl acetate = 3:1, UV 254) indicated starting material was remained and new spots formed. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL *3). The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 45% petroleum ether/ethyl acetate @ 35 mL/min). Compound *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propanamide (645 mg, 66.4% yield, 84% purity) was obtained as a white solid.

[000954] 269A: To a solution of *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[4-oxo-3-(2-trimethylsilylethoxymethyl)imidazo[4,5-c]pyridin-5-yl]propanamide (600 mg, 1.17 mmol, 1 eq) in THF (1 mL) was added TBAF (1 M, 2.3 mL, 2 eq). The mixture was stirred at 60 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40mm*3um;mobile phase: [water(0.05% NH_3H_2O + 10 mM NH_4HCO_3)-ACN];B%: 5%-35%,9.5 min). Compound $C_{19}H_{22}N_6O_3$ (34 mg, 7.6% yield, 100% purity) was obtained as white solid.

[000955] (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-oxo-3H-imidazo[4,5-c]pyridin-5-yl)propanamide (34 mg, 88.9 umol, 1 eq) was purity by SFC. The residue was purified by prep-HPLC (column: (s,s) WHELK-O1 (250mm*30mm,5um);mobile phase: [0.1% NH_3H_2O EtOH];B%: 40%-40%,min).

Compound (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-oxo-3H-imidazo[4,5-c]pyridin-5-yl)propanamide (18.56 mg, 54.5% yield, 100% purity) was obtained as white solid.

[000956] LCMS： Rt = 0.627 min; for $C_{19}H_{22}N_6O_3$ MS Calcd.: 382.42; MS Found: 383.1 [M+H$^+$].

[000957] ^{1}H NMR (400MHz, CD_3OD) δ 9.28 (br s, 1H), 7.94 - 7.79 (m, 1H), 6.86 (br d, *J* = 7.3 Hz, 1H), 5.74 - 5.50 (m, 2H), 4.62 - 4.18 (m, 2H), 3.50 - 3.32 (m, 1H), 3.14 (br s, 1H), 2.66 - 2.37 (m, 1H), 2.28 (br s, 1H), 2.16 - 1.95 (m, 3H), 1.92 - 1.72 (m, 2H), 0.62 (br s, 1H), 0.41 (br d, *J* = 3.8 Hz, 2H), 0.18 (br s, 1H), 0.03 (br d, *J* = 4.5 Hz, 1H).

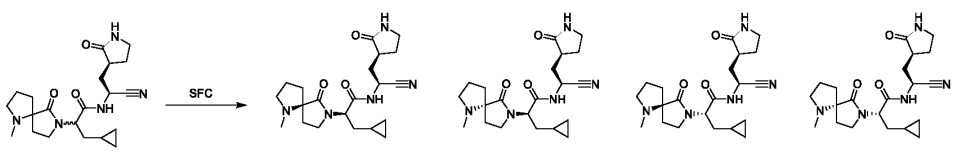
Example 102. Synthesis of viral protease inhibitor compound 269

[000958] (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-oxo-3*H*-imidazo[4,5-c]pyridin-5-yl)propanamide (28 mg, 73.2 umol, 1 eq) was purity by SFC. The residue was purified by prep-HPLC (column: (s,s) WHELK-O1 (250mm*30mm,5um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 40%-40%,min). Compound (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-oxo-3*H*-imidazo[4,5-c]pyridin-5-yl)propanamide (15.52 mg, 55.4% yield, 100% purity) was obtained as a white solid.

[000959] LCMS： Rt = 0.647 min; for $C_{19}H_{22}N_6O_3$ MS Calcd.: 382.42; MS Found: 383.1 [M+H$^+$].

[000960] ^{1}H NMR (400 MHz, CD_3OD) δ 9.29 (br s, 1H), 7.88 (br d, *J* = 6.3 Hz, 1H), 6.87 (br d, *J* = 6.5 Hz, 1H), 5.89 - 5.41 (m, 1H), 4.74 - 4.29 (m, 1H), 3.48 (br s, 1H), 3.30 - 3.09 (m, 1H), 2.67 - 2.42 (m, 1H), 2.39 - 2.21 (m, 1H), 2.21 - 1.99 (m, 3H), 1.94 - 1.55 (m, 1H), 0.63 (br s, 1H), 0.42 (br s, 2H), 0.27 - 0.08 (m, 2H).

Example 103. Synthesis of viral protease inhibitor compound 271 & 271A



[000961] 271A Isomer 1: (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*R*)-1-methyl-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl]propanamide

[000962] 271A Isomer 2: (2*R*)-N-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*S*)-1-methyl-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl]propanamide

[000963] 271 Isomer 3: (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*R*)-1-methyl-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl]propanamide

[000964] 271 Isomer 4: (2*S*)-N-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*S*)-1-methyl-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl]propanamide

[000965] 270 was purified by *prep*-SFC (column: DAICEL CHIRALPAK AS(250mm*30mm,10um);mobile phase: [0.1%NH3H2O ETOH];B%: 20%-20%,min) to give 271A (30 mg) and 271 (20 mg). 271A Isomer 1 & 2 was purified by prep-SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O IPA];B%: 25%-25%,min) to give 271A Isomer 1 (2.65 mg, 2% yield) and 271A Isomer 2 (2.76 mg, 2% yield) as two white solid. 271 Isomer 1 & 271 Isomer 2 was purified by prep-SFC (column: DAICEL CHIRALPAK IG (250mm*30mm, 10um); mobile phase: [0.1%NH_3H_2O MEOH]; B%: 40%-40%, min) to give 271 Isomer 1 (15.96 mg, 15% yield) and 271 Isomer 2 (13.71 mg, 13% yield) as two white solid.

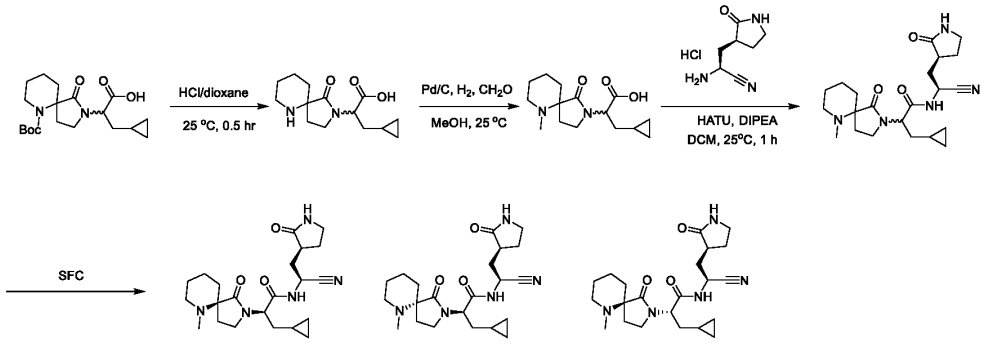
[000966] 271A Isomer 1: LCMS： Rt = 1.208 min; for $C_{21}H_{31}N_5O_3$ MS Calcd.: 401.24; MS Found: 402.2 [M+H^+]; ^{1}H NMR (400MHz, CD_3OD) δ 4.96 (dd, *J* = 6.8, 9.3 Hz, 1H), 4.66 - 4.61 (m, 1H), 3.50 (dd, *J* = 5.6, 8.1 Hz, 2H), 3.37 - 3.31 (m, 2H), 3.11 - 3.02 (m, 1H), 2.91 - 2.81 (m, 1H), 2.53 - 2.42 (m, 1H), 2.40 - 2.31 (m, 4H), 2.30 - 2.09 (m, 3H), 2.02 - 1.81 (m, 7H), 1.61 (td, *J* = 7.2, 14.1 Hz, 1H), 0.69 - 0.60 (m, 1H), 0.55 - 0.40 (m, 2H), 0.20 - 0.13 (m, 2H).

[000967] 271A Isomer 2: LCMS： Rt = 1.180 min; for $C_{21}H_{31}N_5O_3$ MS Calcd.: 401.24; MS Found: 402.2 [M+H^+]; ^{1}H NMR (400MHz, CD_3OD) δ 5.01 (dd, *J* = 6.3, 9.9 Hz, 1H), 4.57 (t, *J* = 7.8 Hz, 1H), 3.55 - 3.47 (m, 2H), 3.37 - 3.31 (m, 2H), 3.11 - 2.99 (m, 1H), 2.90 - 2.80 (m, 1H), 2.60 - 2.46 (m, 1H), 2.37 - 2.14 (m, 6H), 2.09 - 1.72 (m, 8H), 1.63 - 1.50 (m, 1H), 0.74 - 0.63 (m, 1H), 0.58 - 0.44 (m, 2H), 0.24 - 0.15 (m, 2H).

[000968] 271 Isomer 1: LCMS: Rt = 1.217 min; for $C_{21}H_{31}N_5O_3$ MS Calcd.: 401.24; MS Found: 402.2 [M+H$^+$]; ^{1}H NMR (400MHz, CD_3OD) δ 5.04 - 4.92 (m, 1H), 4.67 - 4.60 (m, 1H), 3.73 - 3.39 (m, 2H), 3.37 - 3.32 (m, 2H), 3.15 - 3.00 (m, 1H), 2.88 (d, *J* = 6.5 Hz, 1H), 2.62 - 2.42 (m, 1H), 2.40 - 2.15 (m, 6H), 2.11 - 1.76 (m, 8H), 1.68 - 1.51 (m, 1H), 0.75 - 0.57 (m, 1H), 0.57 - 0.39 (m, 2H), 0.23 - 0.11 (m, 2H).

[000969] 271 Isomer 2: LCMS: Rt = 1.222 min; for $C_{21}H_{31}N_5O_3$ MS Calcd.: 401.24; MS Found: 402.2 [M+H$^+$]; ^{1}H NMR (400MHz, CD_3OD) δ 5.01 (dd, *J* = 6.1, 9.9 Hz, 1H), 4.56 (t, *J* = 7.8 Hz, 1H), 3.70 - 3.61 (m, 1H), 3.49 - 3.40 (m, 1H), 3.37 - 3.32 (m, 1H), 3.30 - 3.23 (m, 1H), 3.06 - 2.98 (m, 1H), 2.87 - 2.77 (m, 1H), 2.53 (dq, J = 5.5, 9.3 Hz, 1H), 2.37 - 2.16 (m, 6H), 2.10 - 1.75 (m, 8H), 1.65 - 1.54 (m, 1H), 0.72 - 0.61 (m, 1H), 0.57 - 0.46 (m, 2H), 0.21 - 0.11 (m, 2H).

Example 104. Synthesis of viral protease inhibitor compound 273A, 273B & 273C



Step 1: 3-cyclopropyl-2-(1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propanoic acid

[000970] A solution of 1 (0.7 g, 1.91 mmol, 1 eq) in HCl/dioxane (4 M, 10 mL, 20.9 eq) was stirred at 25 °C for 0.5 hr. LC-MS showed 1 was consumed completely and 45% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 3-cyclopropyl-2-(1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propanoic acid (500 mg, crude) was obtained as a colorless oil.

Step 2: (2S)-3-cyclopropyl-2-(6-methyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propanoic acid

[000971] A solution of 3-cyclopropyl-2-(1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propanoic acid (0.5 g, 1.88 mmol, 1 eq) in MeOH (4 mL) was added Pd/C (50 mg, 0.37 mmol,

10% purity) and formaldehyde (1.52 g, 18.7 mmol, 1.4 mL, 37% purity, 10 *eq*) was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 0.5 hour. One spot was detected on TLC (Dichloromethane: Methanol=5/1, $KMnO_4$). LC-MS showed 2 was consumed completely and 71% of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, dichloromethane: methanol =100/1 to 5/1) to give (2S)-3-cyclopropyl-2-(6-methyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propanoic acid (0.4 g, 76% yield) as a white solid.

Step 3: (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(6-methyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propanamide

[000972] To a solution of (2S)-3-cyclopropyl-2-(6-methyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propanoic acid (0.3 g, 1.0 mmol, 1 eq) in DCM (6 mL) was added HATU (610.3 mg, 1.61 mmol, 1.5 eq), DIPEA (276.5 mg, 2.14 mmol, 0.37 mL, 2.0 eq), and 3a (243.51 mg, 1.28 mmol, 1.2 eq, HCl). The mixture was stirred at 25 °C for 1 hr. LC-MS showed 3 was consumed completely and 15% of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40mm*3um; mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 17%-47%, 9.5 min) to give (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(6-methyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propanamide (60 mg, 13% yield) as a white solid.

[000973] 273A: (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*R*)-6-methyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl]propanamide

[000974] 273B: (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*S*)-6-methyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl]propanamide

[000975] 273C: (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*R*)-6-methyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl]propanamide

[000976] 4 was purified by prep-SFC (column: DAICEL CHIRALPAK AS(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 20%-20%,min) to

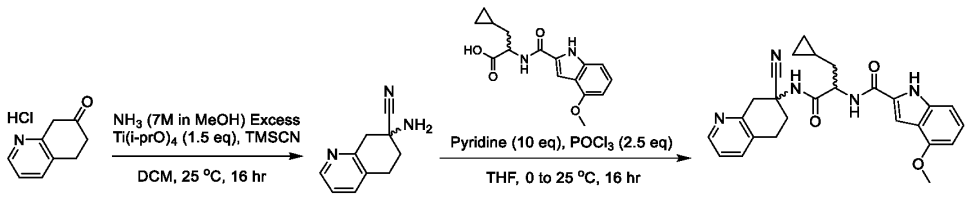
give 273A & 273B (20 mg) and 273C (2.79 mg, 6.5 umol, 4% yield, 97% purity). 273A & 273B (20 mg) was purified by prep-SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 40%-40%,min) to give 273A (2.50 mg, 4.1% yield) and 273B (2.59 mg, 4% yield).

[000977] 273A: LCMS: Rt = 1.362 min; for $C_{22}H_{33}N_5O_3$ MS Calcd.: 415.26; MS Found: 416.2 [M+H^+]. ^{1}H NMR (400MHz, CD_3OD) δ 4.79 (s, 1H), 4.52 - 4.47 (m, 1H), 3.34 - 3.24 (m, 2H), 3.20 - 3.15 (m, 2H), 2.60 - 2.44 (m, 1H), 2.35 - 2.24 (m, 1H), 2.22 - 2.00 (m, 4H), 1.94 (s, 3H), 1.83 - 1.64 (m, 4H), 1.60 - 1.31 (m, 7H), 0.55 - 0.38 (m, 1H), 0.37 - 0.20 (m, 2H), 0.06 - 0.12 (m, 2H).

[000978] 273B: LCMS: Rt = 1.353 min; for $C_{22}H_{33}N_5O_3$ MS Calcd.: 415.26; MS Found: 416.2 [M+H^+]. ^{1}H NMR (400MHz, CD_3OD) δ 4.83 (dd, *J* = 6.8, 9.3 Hz, 1H), 4.52 - 4.49 (m, 1H), 3.47 - 3.38 (m, 1H), 3.34 - 3.25 (m, 1H), 3.23 - 3.17 (m, 2H), 2.60 - 2.50 (m, 1H), 2.41 - 2.27 (m, 1H), 2.25 - 2.03 (m, 4H), 1.97 (s, 3H), 1.82 - 1.31 (m, 11H), 0.50 - 0.40 (m, 1H), 0.37 - 0.23 (m, 2H), 0.05 -0.06 (m, 2H).

[000979] 273C: LCMS: Rt = 1.363 min; for $C_{22}H_{33}N_5O_3$ MS Calcd.: 415.26; MS Found: 416.2 [M+H^+]. ^{1}H NMR (400MHz, CD_3OD) δ 4.82 (dd, *J* = 6.0, 10.0 Hz, 1H), 4.42 - 4.38 (m, 1H), 3.41 - 3.23 (m, 2H), 3.18 - 3.14 (m, 1H), 3.12 - 3.06 (m, 1H), 2.57 - 2.46 (m, 1H), 2.45 - 2.29 (m, 1H), 2.17 - 1.95 (m, 4H), 1.93 (s, 3H), 1.80 - 1.58 (m, 4H), 1.57 - 1.26 (m, 7H), 0.57 - 0.41 (m, 1H), 0.40 - 0.23 (m, 2H), 0.06 - 0.07 (m, 2H).

Example 105. Synthesis of viral protease inhibitor compound 278



7-Amino-5,6,7,8-tetrahydroquinoline-7-carbonitrile

[000980] A solution of 6,8-dihydro-5*H*-quinolin-7-one (350 mg, 1.91 mmol, 1 *eq*, HCl) in DCM (7 mL) were added NH_3 (7 M, 2.72 mL, 10 *eq*) and Ti(i-PrO)$_4$ (650.0 mg, 2.29 mmol, 0.67 mL, 1.2 *eq*) was stirred at 25 °C for 2 hr. TMSCN (283.6 mg, 2.86 mmol,

0.35 mL, 1.5 *eq*) was added and the solution was stirred at 25 °C for 16 hr. LC-MS showed starting material was consumed completely and one main peak with desired MS was detected. Ethyl acetate (50 mL) and H_2O (2.0 mL) were added, the reaction mixture was filtered, the filtrate was concentrated to reduce pressure. Compound 7-amino-6,8-dihydro-5*H*-quinoline-7-carbonitrile (260 mg, crude) was obtained as a yellow solid.

[000981] 278: *N*-(1-((7-Cyano-5,6,7,8-tetrahydroquinolin-7-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide

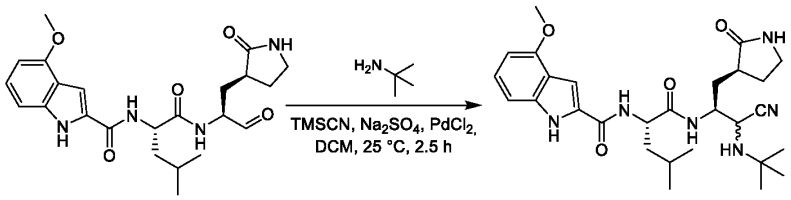
[000982] A solution of 7-amino-6,8-dihydro-5*H*-quinoline-7-carbonitrile (80 mg, 0.46 mmol, 1 *eq*), (2*S*)-3-cyclopropyl-2-[(4-methoxy-1*H*-indole-2-carbonyl)amino]propanoic acid (153.5 mg, 0.50 mmol, 1.1 *eq*) and pyridine (365.3 mg, 4.62 mmol, 0.37 mL, 10 *eq*) in THF (2 mL) was stirred at 25 °C for 15 min. After $POCl_3$ (177.0 mg, 1.15 mmol, 0.10 mL, 2.5 *eq*) was added dropwise at 0 °C, the reaction mixture was stirred at 25 °C for 16 hours. LC-MS showed starting material was remained and one peak with desired MS was detected. The reaction mixture was basified with Sat.$NaHCO_3$ to pH=8 and extracted with ethyl acetate (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 23% - 53%, 9.5 min) to give the title compound as a light yellow solid. Compound *N*-[2-[(7-cyano-6,8-dihydro-5*H*-quinolin-7-yl)amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide (2.32 mg, 1.08% yield, 98.6% purity) was obtained as a light yellow solid.

[000983] LCMS： Rt = 0.754 min; for $C_{26}H_{27}N_5O_3$ MS Calcd.: 457.21; MS Found: 458.1 [$M+H^+$].

[000984] ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 - 8.24 (m, 1H), 7.65 - 7.56 (m, 1H), 7.29 - 7.12 (m, 3H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 4.64 - 4.60 (m, 1H), 3.93 (s, 3H), 3.76 - 3.57 (m, 1H), 3.45 - 3.33 (m, 1H), 3.17 - 2.94 (m, 2H), 2.60 - 2.36 (m, 2H), 1.88 - 1.78 (m, 1H), 1.75 - 1.60 (m, 1H), 0.89 - 0.72 (m, 1H), 0.56 - 0.41 (m, 2H), 0.24 - 0.12 (m, 2H).

[000985] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.79 (d, J = 15.8 Hz, 1H), 8.53 - 8.43 (m, 1H), 8.36 (dd, J = 4.6, 11.4 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 14.3 Hz, 1H), 7.25 - 7.15 (m, 1H), 7.14 - 7.06 (m, 1H), 7.05 - 6.98 (m, 1H), 6.51 (d, J = 7.5 Hz, 1H), 4.61 - 4.45 (m, 1H), 3.89 (s, 3H), 3.59 (d, J = 16.8 Hz, 1H), 3.23 (d, J = 16.8 Hz, 1H), 2.98 - 2.83 (m, 2H), 2.42 (dd, J = 6.1, 12.9 Hz, 1H), 2.36 - 2.18 (m, 1H), 1.87 - 1.68 (m, 1H), 1.57 - 1.34 (m, 1H), 0.88 - 0.64 (m, 1H), 0.46 - 0.25 (m, 2H), 0.23 - 0.01 (m, 2H)

Example 106. Synthesis of viral protease inhibitor compound 323



Step for 323 Isomer 1& 2: N-[(1S)-1-[[(1S)-2-(tert-butylamino)-2-cyano-1-[[(3S)-2-oxopyrrolidin -3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

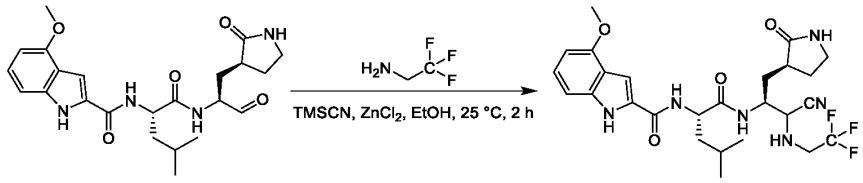
[000986] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl- butyl]-4-methoxy-1H-indole-2-carboxamide (100 mg, 180.79 umol, 80% purity, 1 eq) in DCM (5 mL) was added $PdCl_2$ (6.41 mg, 36.16 umol, 0.2 eq), Na_2SO_4 (89.88 mg, 632.76 umol, 64.20 uL, 3.5 eq) and 2-methylpropan-2-amine (26.44 mg, 361.58 umol, 37.99 uL, 2 eq). The mixture was stirred at 25 °C for 30 min, then added TMSCN (35.87 mg, 361.58 umol, 45.23 uL, 2 eq), the mixture was stirred at 25 °C for 2 h. Upon the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by Hexane-IPA prep-HPLC to get the compound N-[(1S)-1-[[(1S)-2-(tert-butylamino)-2-cyano-1-[[(3S)-2-oxo pyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (16.10 mg, 25.59 umol, 14.16% yield, 83.4% purity) and N-[(1S)-1-[[(1S)-2-(tert-butylamino)- 2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (7.92 mg, 12.27 umol, 6.79% yield, 81.3% purity) as white solid. MS (ESI) m/z 524.8 $[M+H]^+$

[000987] column: Phenomenex luna CN 5u 100*30 mm; mobile phase: [Hexane-IPA];B%: 5%-60%,10 min

[000988] 1H NMR (400 MHz, DMSO-*d*6) δ = 11.57 (s, 1H), 8.45 - 8.35 (m, 1H), 7.98 (d, *J*=9.3 Hz, 1H), 7.56 (s, 1H), 7.42 - 7.30 (m, 1H), 7.15 - 7.05 (m, 1H), 7.03 - 6.96 (m, 1H), 6.50 (d, *J*=7.6 Hz, 1H), 4.51 - 4.41 (m, 1H), 3.99 - 3.91 (m, 1H), 3.88 (s, 3H), 3.63 (dd, *J*=7.7, 10.2 Hz, 1H), 3.16 - 2.99 (m, 2H), 2.37 - 2.21 (m, 1H), 2.16 - 2.03 (m, 1H), 1.90 - 1.45 (m, 6H), 1.05 - 1.00 (m, 9H), 0.97 - 0.84 (m, 6H)

[000989] 1H NMR (400 MHz, DMSO-*d*6) δ = 11.81 - 11.42 (m, 1H), 8.62 - 7.84 (m, 2H), 7.69 - 7.47 (m, 1H), 7.42 - 7.28 (m, 1H), 7.20 - 6.94 (m, 2H), 6.50 (d, *J*=7.6 Hz, 1H), 4.61 - 4.40 (m, 1H), 4.13 - 3.58 (m, 5H), 3.23 - 2.91 (m, 2H), 2.38 - 1.98 (m, 3H), 1.91 - 1.37 (m, 5H), 1.12 - 1.00 (m, 9H), 0.97 - 0.79 (m, 6H)

Example 107. Synthesis of viral protease inhibitor compound 325



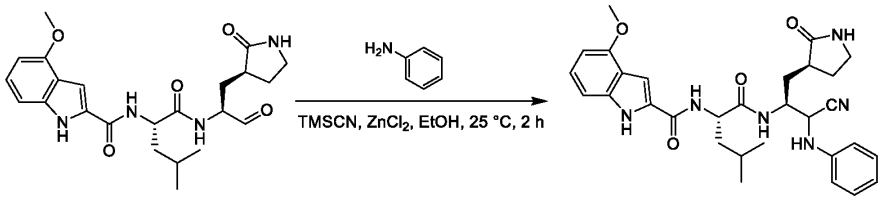
N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2-(2,2,2-trifluoroethylamino)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[000990] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (180 mg, 325.42 umol, 80% purity, 1 eq) in EtOH (2 mL) was added 2,2,2-trifluoroethanamine (64.47 mg, 650.84 umol, 51.17 uL, 2 eq) and $ZnCl_2$ (8.87 mg, 65.08 umol, 3.05 uL, 0.2 eq). The mixture was stirred at 25 °C for 30 min, and then TMSCN (64.57 mg, 650.84 umol, 81.42 uL, 2 eq) was added. The mixture was stirred at 25 °C for 2 h. The residue was purified by HCl prep-HPLC to get the compound N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2-(2,2,2- trifluoroethylamino)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (120 mg, 215.78 umol, 66.31% yield, 99% purity) as a white solid. MS (ESI) *m/z* 551.2 $[M+H]^+$

[000991] Column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.04%HCl)-ACN];B%: 38%-62%,7min

[000992] ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.56 (dd, *J*=2.0, 5.5 Hz, 1H), 8.39 (br t, *J*=8.6 Hz, 1H), 8.32 - 8.16 (m, 1H), 7.59 (br d, *J*=17.6 Hz, 1H), 7.37 (dd, *J*=1.5, 5.7 Hz, 1H), 7.15 - 6.92 (m, 2H), 6.50 (d, *J*=7.7 Hz, 1H), 4.57 - 4.36 (m, 1H), 4.25 - 4.02 (m, 1H), 4.00 - 3.81 (m, 4H), 3.78 - 3.40 (m, 2H), 3.19 - 2.94 (m, 2H), 2.42 - 1.94 (m, 3H), 1.88 - 1.36 (m, 5H), 0.91 (dd, *J*=6.3, 15.1 Hz, 6H).

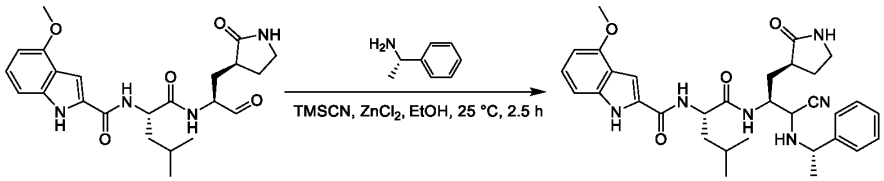
Example 108. Synthesis of viral protease inhibitor compound 327



[000993] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (180 mg, 325.42 umol, 80% purity, 1 eq) in EtOH (4 mL) was added $ZnCl_2$ (8.87 mg, 65.08 umol, 3.05 uL, 0.2 eq) and aniline (60.61 mg, 650.84 umol, 59.42 uL, 2 eq), and the mixture was stirred at 25 °C for 30 min. After the addition of TMSCN (64.57 mg, 650.84 umol, 81.42 uL, 2 eq), the mixture was stirred at 25 °C for 2 h. Upon the reaction was completed. The reaction mixture was filtered to get the product. The reaction mixture was purified by prep-HPLC to get the product N-[(1S)-1-[[(1S)-2-anilino-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (70 mg, 122.10 umol, 37.52% yield, 95% purity) as a white solid. MS (ESI) *m/z* 545.3 $[M+H]^+$

[000994] 1H NMR (400MHz, DMSO-*d*6) δ = 11.59 (br d, *J*=2.0 Hz, 1H), 8.44 (br d, *J*=7.7 Hz, 1H), 8.26 (d, *J*=9.5 Hz, 1H), 7.63 - 7.51 (m, 1H), 7.38 (d, *J*=1.8 Hz, 1H), 7.26 - 6.94 (m, 4H), 6.80 - 6.65 (m, 3H), 6.51 (d, *J*=7.5 Hz, 1H), 6.34 (d, *J*=9.9 Hz, 1H), 4.59 - 4.20 (m, 3H), 3.89 (s, 3H), 3.18 - 2.95 (m, 2H), 2.44 - 2.30 (m, 1H), 2.24 - 2.00 (m, 1H), 1.97 - 1.43 (m, 6H), 0.99 - 0.82 (m, 6H)

Example 109. Synthesis of viral protease inhibitor compound 329

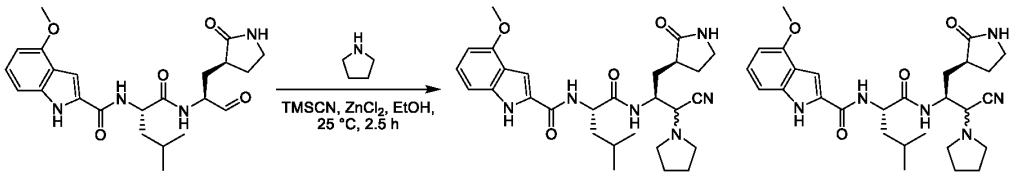


[000995] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (100 mg, 180.79 umol, 80% purity, 1 eq) in EtOH (4 mL) was added (1S)-1-phenylethanamine (43.82 mg, 361.58 umol, 46.02 uL, 2 eq), $ZnCl_2$ (4.93 mg, 36.16 umol, 1.69 uL, 0.2 eq). The mixture was stirred at 25 °C for 30 min, and then TMSCN (35.87 mg, 361.58 umol, 45.24 uL, 2 eq) was added. After stirring the mixture at 25 °C for 2 h, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by HCl prep-HPLC to provide compound N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2-[[(1S)-1-phenylethyl]amino]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (90 mg, 154.01 umol, 85.19% yield, 98% purity) as a white solid. MS (ESI) m/z 573.2 $[M+H]^+$

[000996] column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.04%HCl)-ACN];B%: 40%-70%,7 min

[000997] 1H NMR (400MHz, DMSO-d6) δ = 11.39 (br s, 1H), 8.46 - 7.80 (m, 2H), 7.52 - 6.89 (m, 9H), 6.51 (br d, J=7.5 Hz, 1H), 4.64 - 4.35 (m, 1H), 4.26 - 4.03 (m, 1H), 3.96 - 3.83 (m, 4H), 3.36 - 3.03 (m, 3H), 2.37 - 1.51 (m, 8H), 1.39 - 1.21 (m, 3H), 0.90 (br dd, J=5.7, 14.6 Hz, 6H)

Example 110. Synthesis of viral protease inhibitor compound 331



[000998] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (100 mg, 180.79 umol, 80% purity, 1 eq) in EtOH (4 mL) was added pyrrolidine (25.72 mg, 361.58 umol, 30.18 uL, 2 eq), $ZnCl_2$ (1 M, 1.81 uL, 0.01 eq). The mixture was stirred at 25 °C

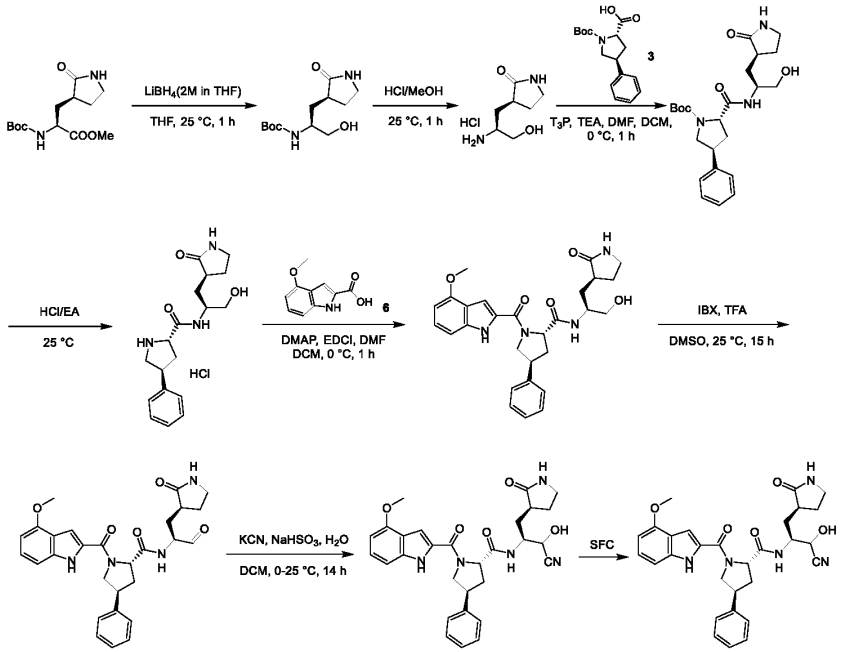
for 30 min, and then was added TMSCN (35.87 mg, 361.58 umol, 45.24 uL, 2 eq). The mixture was stirred at 25 °C for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by Hexane-IPA prep-HPLC to get the compound N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]-2- pyrrolidin-1-yl-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (19.34 mg, 33.19 umol, 18.36% yield, 89.7% purity) and N-[(1S)-1-[[(1S)-2-cyano-1-[[(3S)-2-oxopyrrolidin -3-yl]methyl]-2-pyrrolidin-1-yl-ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (10.41 mg, 13.70 umol, 7.58% yield, 68.8% purity) as white solid. MS (ESI) *m/z* 523.4 $[M+H]^+$

[000999] column: Phenomenex luna CN 5u 100*30mm;mobile phase: [Hexane-IPA];B%: 5%-60%,10min

[0001000] 1H NMR (400MHz, DMSO-*d6*) δ = 11.58 (s, 1H), 8.43 (d, *J*=7.7 Hz, 1H), 8.19 (d, *J*=9.4 Hz, 1H), 7.61 - 7.50 (m, 1H), 7.38 (d, *J*=1.8 Hz, 1H), 7.14 - 6.95 (m, 2H), 6.50 (d, *J*=7.6 Hz, 1H), 4.54 - 4.35 (m, 1H), 4.17 - 4.00 (m, 1H), 3.99 - 3.92 (m, 1H), 3.88 (s, 3H), 3.14 - 2.94 (m, 2H), 2.64 - 2.53 (m, 4H), 2.39 - 2.27 (m, 1H), 2.17 - 2.02 (m, 1H), 1.88 - 1.66 (m, 7H), 1.63 - 1.44 (m, 3H), 0.91 (dd, *J*=6.3, 16.2 Hz, 6H)

[0001001] 1H NMR (400MHz, DMSO-*d6*) δ = 11.56 (br d, *J*=1.8 Hz, 1H), 8.43 - 8.30 (m, 1H), 8.00 (d, *J*=9.2 Hz, 1H), 7.60 (s, 1H), 7.35 (d, *J*=1.8 Hz, 1H), 7.16 - 6.94 (m, 2H), 6.50 (d, *J*=7.6 Hz, 1H), 4.55 - 4.35 (m, 1H), 4.13 - 4.03 (m, 1H), 4.02 - 3.94 (m, 1H), 3.88 (s, 3H), 3.13 - 3.01 (m, 2H), 2.70 - 2.57 (m, 2H), 2.43 - 2.29 (m, 1H), 2.17 - 1.94 (m, 2H), 1.88 - 1.34 (m, 9H), 0.90 (dd, *J*=6.5, 15.2 Hz, 6H)

Example 111. Synthesis of viral protease inhibitor compound 345



Step 1: tert-butyl ((S)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate

[0001002] To a solution of methyl (2*S*)-2-(tert-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (2.00 g, 6.99 mmol, 1 *eq*) in THF (20 mL) was added LiBH4 (2 M, 6.99 mL, 2 *eq*) at 25°C under N_2. The mixture was then stirred at 25 °C for 1 h. The mixture was quenched with NH_4Cl aq. (20.0 mL), and extracted with EtOAc (20.0 mL*5). The organic layers were washed with brine (20.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was triturated with ethyl acetate:petroleum ether=1:2 at 25 °C for 1 h to give *tert*-butyl ((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (1.57 g, crude) as white solid. MS (ESI) *m/z* 259.2 $[M+H]^+$.

Step 2: (S)-3-((S)-2-amino-3-hydroxypropyl)pyrrolidin-2-one

[0001003] A solution of *tert*-butyl ((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (2.39 g, 9.25 mmol, 1 *eq*) in HCl/MeOH (4 M, 23.9 mL, 10.33 *eq*) was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give (*S*)-3-((*S*)-2-amino-3-hydroxypropyl)pyrrolidin-2-one (1.8 g, crude, HCl) as a yellow oil.

Step 3:(2S,4S)-tert-butyl 2-(((S)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate

[0001004] To a solution of (*S*)-3-((*S*)-2-amino-3-hydroxypropyl)pyrrolidin-2-one (1.8 g, 9.25 mmol, 1 *eq*, HCl) in DMF (12 mL) and DCM (6 mL) was added TEA (5.61 g, 55.48 mmol, 7.72 mL, 6 *eq*), (2S,4S)-1-tert-butoxycarbonyl-4-phenyl-pyrrolidine-2-carboxylic acid (2.69 g, 9.25 mmol, 1 *eq*), then T3P (17.65 g, 27.74 mmol, 16.5 mL, 50% purity, 3 *eq*) at 0 °C. After the mixture was stirred at 0 °C for 1 h, the mixture was quenched with water (40 mL) and extracted with EtOAc (20 mL* 5). The organic layers were washed with brine (20.0 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by column chromatography (SiO_2, DCM: MeOH = 10:1 to 1:1) to give (2*S*,4*S*)-*tert*-butyl 2-(((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (3.04 g, 6.69 mmol, 72.38% yield, 95% purity) as yellow solid. MS (ESI) *m/z* 432.2 $[M+H]^+$.

Step 4: (2S,4S)-N-((S)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-phenylpyrrolidine-2-carboxamide

[0001005] A mixture of (2*S*,4*S*)-*tert*-butyl 2-(((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (3.04 g, 7.04 mmol, 1 *eq*) in HCl/EtOAc (4 M, 30 mL, 17.03 *eq*) was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give (2*S*,4*S*)-N-((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-phenylpyrrolidine-2-carboxamide (2.59 g, crude, HCl) as white solid. MS (ESI) *m/z* 332.2 $[M+H]^+$.

Step 5: (2S,4S)-N-((S)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamide

[0001006] To a solution of (2*S*,4*S*)-N-((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-phenylpyrrolidine-2-carboxamide (2.58 g, 7.01 mmol, 1 *eq*, HCl) in DMF (16 mL) and DCM (8 mL) was added 4-methoxy-1H-indole-2-carboxylic acid (1.34 g, 7.01 mmol, 1 *eq*), DMAP (1.71 g, 14.03 mmol, 2 *eq*), and EDCI (2.69 g, 14.03 mmol, 2 *eq*). The mixture was stirred at 0 °C for 1 h. The mixture was quenched with water (50.0 mL) and extracted with EtOAc (20.0 mL* 4). The organic layers were washed with brine (20.0 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by column chromatography (SiO_2, DCM: MeOH = 10:1 to 3:1) to give (2*S*,4*S*)-N-((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-

4-phenylpyrrolidine-2-carboxamide (2.1 g, 3.79 mmol, 54.00% yield, 91% purity) as light yellow solid. MS (ESI) *m/z* 505.1 $[M+H]^+$.

Step 6: (2S,4S)-1-(4-methoxy-1H-indole-2-carbonyl)-N-((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-phenylpyrrolidine-2-carboxamide

[0001007] To a mixture of (2*S*,4*S*)-N-((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamide (200 mg, 376.55 umol, 95% purity, 1 *eq*) in DMSO (2 mL) was added TFA (64.40 mg, 564.83 umol, 41.82 uL, 1.5 *eq*) and IBX (332.97 mg, 1.13 mmol, 95% purity, 3 *eq*), the mixture was stirred at 25 °C for 14 h. The mixture was quenched with $NaHCO_3$ aq. (15.0 mL) and extracted with EtOAc (10.0 mL* 3). The organic layers were washed with brine (10.0 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by prep-HPLC to give (2*S*,4*S*)-1-(4-methoxy-1H-indole-2-carbonyl)-N-((*S*)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-phenylpyrrolidine-2-carboxamide (58 mg, 111.95 umol, 29.73% yield, 97.0% purity) as white solid. MS (ESI) *m/z* 503.2 $[M+H]^+$.

[0001008] prep-HPLC condition: column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 20%-50%,10min.

[0001009] ^1H NMR (400MHz, DMSO-d_6) δ ppm 11.66 - 11.41 (m, 1H), 9.51 - 7.92 (m, 1H), 7.82 - 7.47 (m, 1H), 7.43 - 7.20 (m, 5H), 7.17 - 6.98 (m, 2H), 6.98 - 6.78 (m, 1H), 6.55 - 6.39 (m, 1H), 5.83 - 5.67 (m, 1H), 4.84 - 4.59 (m, 1H), 4.48 - 4.35 (m, 1H), 4.32 - 4.12 (m, 1H), 3.94 - 3.66 (m, 4H), 3.64 - 3.39 (m, 1H), 3.20 - 3.03 (m, 1H), 2.98 - 2.54 (m, 1H), 2.47 - 2.12 (m, 3H), 2.03 - 1.78 (m, 1H), 1.72 - 1.22 (m, 2H)

Step 7: (2S,4S)-N-((2S)-1-cyano-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamide

[0001010] To a mixture of (2*S*,4*S*)-1-(4-methoxy-1H-indole-2-carbonyl)-N-((*S*)-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-phenylpyrrolidine-2-carboxamide (90 mg, 179.08 umol, 1 *eq*) in DCM (1 mL) was added a solution of $NaHSO_3$ (74.54 mg, 716.33 umol, 50.37 uL, 4 *eq*) in H2O (0.5 mL), and then KCN (46.64 mg, 716.33 umol, 30.69 uL, 4 *eq*) at 0° C. The mixture was stirred at 25 °C for 14 h. The mixture was quenched with water (15.0 mL) and extracted with EtOAc (10.0 mL* 3). The organic layers were

washed with brine (10.0 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by prep-HPLC to give (2*S*,4*S*)-N-((2*S*)-1-cyano-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamide (29 mg, 54.76 umol, 30.58% yield, 100% purity) as white solid. MS (ESI) *m/z* 530.2 $[M+H]^+$.

[0001011] prep-HPLC condition: column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.04%HCl)-ACN];B%: 32%-48%,7min.

[0001012] ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 11.66 - 11.42 (m, 1H), 8.63 - 8.22 (m, 1H), 7.62 (d, *J* = 5.6 Hz, 0.5H), 7.44 (s, 0.5H), 7.41 - 7.29 (m, 4H), 7.29 - 7.21 (m, 1H), 7.15 - 7.07 (m, 1H), 7.06 - 6.99 (m, 1H), 6.98 - 6.92 (m, 0.5H), 6.86 - 6.78 (m, 0.5H), 6.70 (s, 1H), 6.53 - 6.41 (m, 1H), 5.32 - 5.18 (m, 0.5H), 4.86 - 4.66 (m, 0.5H), 4.66 - 4.54 (m, 0.5H), 4.45 - 4.34 (m, 1H), 4.24 - 4.15 (m, 0.5H), 4.12 - 3.96 (m, 1H), 3.95 - 3.87 (m, 0.5H), 3.87 - 3.76 (m, 3H), 3.76 - 3.66 (m, 0.5H), 3.64 - 3.56 (m, 0.5H), 3.52 - 3.42 (m, 1H), 3.20 - 3.09 (m, 1H), 2.85 - 2.74 (0.5, 1H), 2.62 - 2.54 (m, 0.5H), 2.46 - 2.35 (m, 1.5H), 2.30 - 1.98 (m, 2H), 1.92 - 1.80 (m, 0.5H), 1.68 - 1.19 (m, 2.5H).

Step 8: (2S,4S)-N-((2S)-1-cyano-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamide

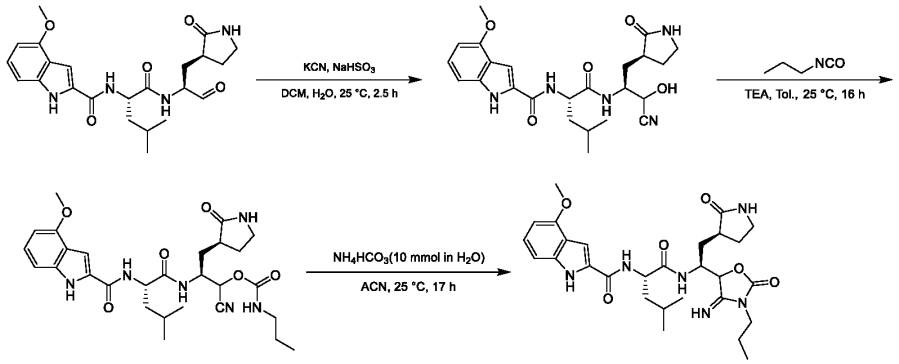
[0001013] (2*S*,4*S*)-N-((2*S*)-1-cyano-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamide (27 mg, 50.98 umol, 1 *eq*) was purified by SFC separation to give (2*S*,4*S*)-N-((2*S*)-1-cyano-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamide (13.03 mg, 22.71 umol, 44.54% yield, 92.3% purity) as a white solid. MS (ESI) *m/z* 530.2 $[M+H]^+$, (2*S*,4*S*)-N-((2*S*)-1-cyano-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamide (12.12 mg, 19.86 umol, 38.96% yield, 86.8% purity) as white solid. MS (ESI) *m/z* 530.2 $[M+H]^+$.

[0001014] Isomer 1: ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 11.64 - 11.47 (m, 1H), 8.62 - 8.30 (m, 1H), 7.64 (s, 0.5H), 7.45 (s, 0.5H), 7.42 - 7.30 (m, 4H), 7.30 - 7.21 (m, 1H), 7.16 - 7.06 (m, 1H), 7.05 - 6.99 (m, 1H), 6.97 - 6.92 (m, 0.5H), 6.86 - 6.80 (m, 0.5H), 6.75 - 6.65 (m, 1H), 6.53 - 6.41 (m, 1H), 5.32 - 5.23 (m, 0.5H), 4.85 - 4.78 (m, 0.5H), 4.66 -

4.54 (m, 1H), 4.45 - 4.35 (m, 0.5H), 4.24 - 4.14 (m, 0.5H), 4.13 - 3.98 (m, 1H), 3.95 - 3.87 (m, 0.5H), 3.87 - 3.75 (m, 3H), 3.75 - 3.66 (m, 0.5H), 3.64 - 3.56 (m, 0.5H), 3.53 - 3.41 (m, 0.5H), 3.22 - 3.11 (m, 1H), 2.80 (t, J = 8.8 Hz, 0.5H), 2.62 - 2.53 (m, 0.5H), 2.46 - 2.36 (m, 2H), 2.29 - 2.15 (m, 1.5 H), 2.14 - 1.97 (m, 1H), 1.69 - 1.54 (m, 0.5H), 1.51 - 1.12 (m, 2.5H)

[0001015] Isomer 2: ^{1}H NMR (400MHz, DMSO- d_6) δ ppm 11.64 - 11.506 (m, 1H), 8.48 (d, J = 9.6 Hz, 0.5H), 8.29 (d, J =9.6 Hz, 0.5H), 7.62 (s, 0.5H), 7.44 (s, 0.5H), 7.40 - 7.31 (m, 4H), 7.29 - 7.23 (m, 1H), 7.11 (q, J = 8.4 Hz, 1H), 7.05 - 6.99 (m, 1H), 6.98 - 6.94 (s, 0.5H), 6.84 - 6.78 (m, 0.5H), 6.77 - 6.69 (m, 1H), 6.52 - 6.42 (m, 1H), 5.23 (d, J = 7.2 Hz, 0.5H), 4.70 (d, J = 6.8 Hz, 0.5H), 4.48 - 4.32 (m, 1H), 4.26 - 4.15 (m, 0.5H), 4.13 - 3.95 (m, 1H), 3.94 - 3.88 (m, 0.5H), 3.86 - 3.76 (m, 3H), 3.76 - 3.69 (m, 0.5H), 3.66 - 3.53 (m, 0.5H), 3.51 - 3.40 (m, 0.5H), 3.20 - 3.09 (m, 1H), 2.84 - 2.74 (m, 1H), 2.45 - 2.35 (m, 2H), 2.31 - 2.11 (m, 2H), 1.92 - 1.80 (m, 1H), 1.60 - 1.21 (m, 3H)

Example 112. Synthesis of viral protease inhibitor compound 355



Step 1: N-((2S)-1-(((2S)-1-cyano-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001016] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (150 mg, 338.98 umol, 1 eq) in DCM (2 mL) was added saturated $NaHSO_3$ (35.27 mg, 338.98 umol, 23.83 uL, 1 eq), and the mixture was stirred at 25 °C for 30 min. A solution of KCN (100 mg, 1.54 mmol, 65.79 uL, 4.53 eq) in H_2O (0.5 mL) was added, and the mixture was stirred at 25 °C for 2 h. Upon completion, the organic phase was collected

and the aqueous layer was extracted with DCM (30 mL * 3). The combined organic phase was washed with brine (30 mL * 2), dried over Na_2SO_4, and concentrated to get the crude. The liquid water was added NaOH to pH=9, then quenched by aq NaClO, then added NaOH to pH > 14. The crude was used to next step directly and without further purification. N-[(1S)-1-[[(1S)-2-cyano-2-hydroxy-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (140 mg, crude) was obtained as yellow solid. MS (ESI) *m/z* 470.1 $[M+H]^+$.

Step 2: (2S)-1-cyano-2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propyl propylcarbamate

[0001017] A solution of 1-isocyanatopropane (27.19 mg, 319.47 umol, 30.21 uL, 5 eq) in dry toluene (0.1 mL) was added dropwise to a solution of the N-[(1S)-1-[[(1S)-2-cyano-2-hydroxy-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (30 mg, 63.89 umol, 1 eq) in dry toluene (0.5 mL) at 0 °C, then the TEA (64.65 ug, 6.39e-1 umol, 8.89e-2 uL, 0.01 eq) was added and the solution was stirred at 25 °C for 17 h under N_2. Upon completion, the solution was concentrated to give the crude. The residue was purified by prep-HPLC (FA condition), column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (0.2%FA)-ACN]; B%: 30%-80%, 8min. [(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl) amino]-4-methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propyl] N-propylcarbamate (8 mg, 14.15 umol, 22.15% yield, 98.124% purity) was obtained as white solid.

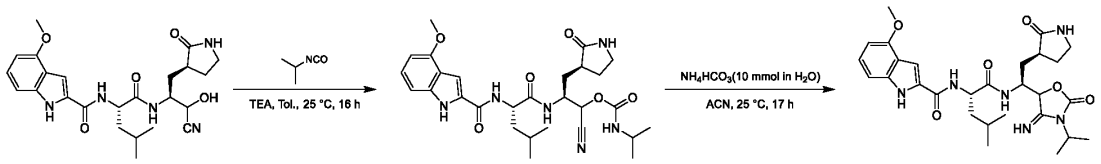
[0001018] ^1H NMR (400MHz, METHANOL-d_4) δ = 7.27 (s, 1H), 7.19 - 7.10 (m, 1H), 7.02 (d, *J*=8.3 Hz, 1H), 6.51 (d, *J*=7.7 Hz, 1H), 5.48 - 5.40 (m, 1H), 4.64 - 4.53 (m, 1H), 4.46 - 4.34 (m, 1H), 3.93 (s, 3H), 3.29 - 3.19 (m, 2H), 3.15 - 3.03 (m, 2H), 2.72 - 2.57 (m, 1H), 2.34 - 2.11 (m, 2H), 1.89 - 1.44 (m, 7H), 1.07 - 0.88 (m, 9H). MS (ESI) *m/z* 555.3 $[M+H]^+$.

Step 3: N-((2S)-1-(((1S)-1-(4-imino-2-oxo-3-propyloxazolidin-5-yl)-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001019] A mixture of [(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl) amino]-4-methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propyl] N-propylcarbamate (50 mg, 90.15 umol, 1 *eq*) in NH_4HCO_3 (0.01 M, 45.07 mL, 5 *eq*) and

ACN (5 mL) was stirred at 25 °C for 17 h. Upon completion, the solution was extracted with EA(40 mL*3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-HPLC, column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 25%-55%, 8min. N-[(1S)-1-[[(1S)-1-(4-imino-2-oxo-3-propyl-oxazolidin-5-yl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (20 mg, 34.21 umol, 16.06% yield, 94.871% purity) was obtained as white solid. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.31 - 7.21 (m, 1H), 7.19 - 7.10 (m, 1H), 7.06 - 6.98 (m, 1H), 6.56 - 6.46 (m, 1H), 5.16 - 5.03 (m, 1H), 4.79 - 4.37 (m, 2H), 3.96 - 3.88 (m, 3H), 3.58 - 3.40 (m, 2H), 3.28 - 3.13 (m, 2H), 2.65 - 2.51 (m, 1H), 2.41 - 2.05 (m, 2H), 1.90 - 1.40 (m, 7H), 1.07 - 0.87 (m, 9H).

Example 113. Synthesis of viral protease inhibitor compound 357



Step 1: (2S)-1-cyano-2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propyl isopropylcarbamate

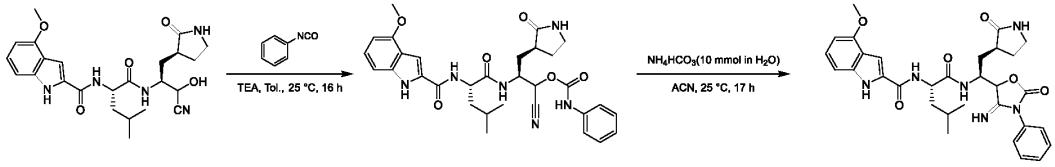
[0001020] A solution of 2-isocyanatopropane (10.88 mg, 127.79 umol, 12.53 uL, 3 eq) in dry toluene (0.1 mL) was added dropwise to a solution of the N-[(1S)-1-[[(1S)-2-cyano-2-hydroxy-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (20 mg, 42.60 umol, 1 eq) in dry toluene (0.5 mL) at 0 °C. After the addition of TEA (4.31 mg, 42.60 umol, 5.93 uL, 1 eq), the solution was stirred at 25 °C for 16 h under dry argon atmosphere. Upon completion, the solution was concentrated to remove the toluene. The residue was purified by prep-HPLC (FA condition), column: Phenomenex Luna C18 75*30 mm*3 um; mobile phase: [water (0.2% FA)-ACN]; B%: 30%-70%, 8 min. [(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl) amino]-4-methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propyl] N-isopropylcarbamate (8 mg, 14.30 umol, 33.57% yield, 99.129% purity) was obtained as white solid.

[0001021] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.27 (s, 1H), 7.19 - 7.10 (m, 1H), 7.02 (d, *J*=8.4 Hz, 1H), 6.51 (d, *J*=7.7 Hz, 1H), 5.48 - 5.39 (m, 1H), 4.64 - 4.53 (m, 1H), 4.44 - 4.33 (m, 1H), 3.93 (s, 3H), 3.80 - 3.64 (m, 1H), 3.28 - 3.17 (m, 2H), 2.72 - 2.58 (m, 1H), 2.34 - 2.10 (m, 2H), 1.88 - 1.58 (m, 5H), 1.23 - 1.09 (m, 6H), 1.01 (td, *J*=5.7, 11.5 Hz, 6H). MS (ESI) *m/z* 555.3 $[M+H]^+$.

Step 2: N-((2S)-1-(((1S)-1-(4-imino-3-isopropyl-2-oxooxazolidin-5-yl)-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001022] [(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl) amino]-4-methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propyl] N-isopropylcarbamate (110 mg, 198.33 umol, 1 eq) in NH_4HCO_3 (0.01 M, 30 mL, 1.51 eq) /ACN (5 mL) was stirred at 25 °C for 17 h. Upon completion, the solution was extracted with ethyl acetate (30 mL*3); the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-HPLC (neutral condition), column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (10mM NH4HCO3)-ACN]; B%: 20%-50%, 8min. N-[(1S)-1-[[(1S)-1-(4-imino-3-isopropyl-2-oxo-oxazolidin-5-yl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (27 mg, 48.55 umol, 24.48% yield, 99.738% purity) was obtained as white solid. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.33 - 7.21 (m, 1H), 7.19 - 7.10 (m, 1H), 7.07 - 6.97 (m, 1H), 6.57 - 6.46 (m, 1H), 5.06 - 4.96 (m, 1H), 4.73 (br d, *J*=11.2 Hz, 1H), 4.64 - 4.53 (m, 1H), 4.44 - 4.28 (m, 1H), 3.96 - 3.89 (m, 3H), 3.27 - 3.15 (m, 2H), 2.66 - 2.49 (m, 1H), 2.43 - 2.15 (m, 2H), 1.85 - 1.24 (m, 4H), 1.07 - 0.91 (m, 6H)

Example 114. Synthesis of viral protease inhibitor compound 359



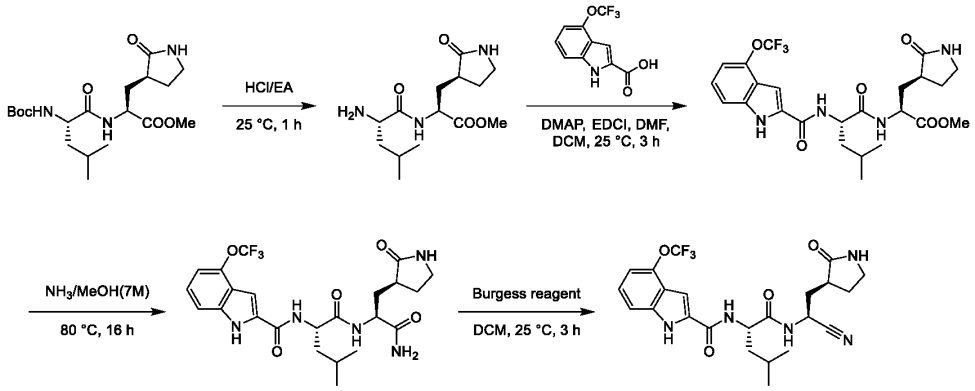
Step 1: (2S)-1-cyano-2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl) propyl phenylcarbamate

[0001023] A solution of isocyanatobenzene (127 mg, 1.07 mmol, 115.32 uL, 5 eq) in dry toluene (0.2 mL) was added dropwise to a solution of the N-[(1S)-1-[[(1S)-2-cyano-2-hydroxy-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (100 mg, 212.98 umol, 1 eq) in dry toluene (1 mL) at 0 °C, and then the TEA (215.51 ug, 2.13 umol, 2.96e-1 uL, 0.01 eq) was added. After the solution was stirred at 25 °C for 16 h under dry argon atmosphere, the solution was quenched with H_2O (10 mL), extracted with ethyl acetate (20 mL * 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The crude was used to next step directly and without further purification. (2S)-1-cyano-2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl) propyl phenylcarbamate (50 mg, 84.94 umol, 1 *eq*) was obtained as white solid. MS (ESI) *m/z* 589.2 $[M+H]^+$.

Step 2: N-[(1S)-1-[[(1S)-1-(4-imino-2-oxo-3-phenyl-oxazolidin-5-yl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[0001024] [(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl) amino]-4-methyl-pentanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propyl] N-phenylcarbamate (50 mg, 84.94 umol, 1 *eq*) in the solution of NH_4HCO_3 (0.01 M, 42.47 mL, 5 *eq*) and ACN (3 mL) was stirred at 25 °C for 17 h. Upon completion, the solution was extracted with ethyl acetate(40 mL * 3), and the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude, the residue was purified by prep-HPLC (neutral condition), column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-50%,8min. N-[(1S)-1-[[(1S)-1-(4-imino-2-oxo-3-phenyl-oxazolidin-5-yl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (6 mg, 9.70 umol, 11.42% yield, 95.16% purity) was obtained as white solid. ^1H NMR (400MHz, METHANOL-d_4) δ = 7.60 - 7.38 (m, 4H), 7.38 - 7.20 (m, 2H), 7.18 - 7.10 (m, 1H), 7.07 - 6.98 (m, 1H), 6.55 - 6.46 (m, 1H), 5.29 - 5.15 (m, 1H), 4.85 - 4.74 (m, 1H), 4.61 - 4.47 (m, 1H), 3.98 - 3.87 (m, 3H), 3.29 - 3.18 (m, 2H), 2.72 - 2.56 (m, 1H), 2.48 - 2.20 (m, 2H), 1.91 - 1.42 (m, 5H), 1.08 - 0.85 (m, 6H) MS (ESI) *m/z* 589.3 $[M+H]^+$.

Example 115. Synthesis of viral protease inhibitor compound 361



Step 1: methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001025] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.25 mmol, 1 *eq*) in HCl/EtOAc (20 mL) was stirred at 25 °C for 1 h. TLC showed the reaction was finished. The reaction was concentrated to give the crude methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (360 mg, crude) as colorless oil. Crude product was used directly without further purification. MS (ESI) *m/z* 299.2 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-4-methyl-2-[[4-(trifluoromethoxy)-1H-indole-2-carbonyl]amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001026] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 901.91 umol, 90% purity, 1 *eq*) and 4-(trifluoromethoxy)-1H-indole-2-carboxylic acid (221.11 mg, 901.91 umol, 1 *eq*) in DCM (12 mL) and DMF (4 mL) was added EDCI (691.58 mg, 3.61 mmol, 4 *eq*) and DMAP (440.74 mg, 3.61 mmol, 4 *eq*). The mixture was stirred at 25 °C and stirred for 3 hours.

[0001027] LCMS showed the reaction was finished. The residue was concentrated in vacuum. The residue was purified by prep-HPLC (column: Kromasil C18 (250* 50mm*10 um); mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-70%, 10 min) to give methyl (2S)-2-[[(2S)-4-methyl-2-[[4-(trifluoromethoxy)-1H-indole-2-carbonyl]amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 427.35 umol, 47.38% yield, 90% purity) as white solid. MS (ESI) *m/z* 526.2 $[M+H]^+$

Step 3: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide

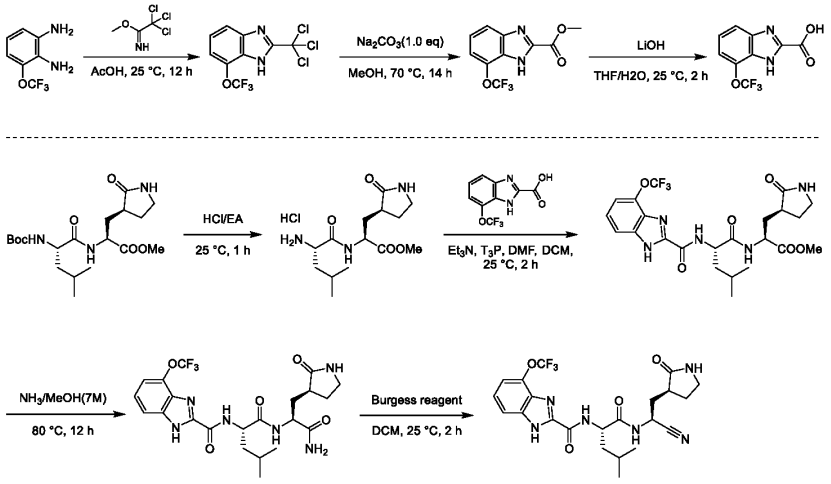
[0001028] A mixture of methyl (2S)-2-[[(2S)-4-methyl-2-[[4-(trifluoromethoxy)-1H-indole-2-carbonyl]amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 474.83 umol, 1 *eq*) in ammonia (29.14 g, 1.71 mol, 28.57 mL, 3603.85 *eq*) was stirred at 80 °C and stirred for 16 hours. LCMS showed the reaction was finished. The reaction was concentrated to give the crude N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide (200 mg, crude) (white solid). Crude product was used directly without further purification. MS (ESI) *m/z* 511.2 $[M+H]^+$

Step 4: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide

[0001029] To a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide (35 mg, 68.43 umol, 1 *eq*) in DCM (2 mL) was added Burgess reagent (65.23 mg, 273.71 umol, 4 *eq*). The mixture was stirred at 25 °C and stirred for 3 hours. LCMS and HPLC showed the reaction was finished. The reaction was concentrated and purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75* 30 mm* 3 um; mobile phase: [water(10mm NH_4HCO_3)-ACN]; B%: 35 %-55 %, 8min) to give N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide (10.02 mg, 20.30 umol, 29.67% yield, 100% purity) (white solid). MS (ESI) *m/z* 493.2 $[M+H]^+$

[0001030] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 12.04 (s, 1 H), 8.94- 9.08 (m, 1 H), 8.72- 8.74 (d, *J*=7.60 Hz, 1 H), 7.71- 7.76 (m, 1 H), 7.44 – 7.46 (d, *J*=7.60 Hz, 2 H), 7.21 -7.23 (m, 1 H), 7.02 – 7.05 (d, *J*=7.60 Hz, 1 H), 4.97 – 5.01 (m, 1 H), 4.47 – 4.50 (m, 1 H), 3.10- 3.14 (m, 2 H), 2.14- 2.15 (m, 1 H), 2.01 – 2.10 (m, 2 H), 1.67 – 1.70 (m, 1 H) 1.67 – 1.70 (m, 1 H)， 1.69 – 1.72 (m, 4 H)，0.92 – 0.95 (m, 3 H)，1.69 – 1.72 (m, 3 H)，

Example 116. Synthesis of viral protease inhibitor compound 363



Step 1: 2-(trichloromethyl)-7-(trifluoromethoxy)-1H-benzo[d]imidazole

[0001031] To a solution of 3-(trifluoromethoxy)benzene-1,2-diamine (500 mg, 2.60 mmol, 1 eq) in AcOH (15 mL) was added drop-wise methyl 2,2,2-trichloroethanimidate (459.12 mg, 2.60 mmol, 321.06 uL, 1.00 eq), and then the reaction was stirred at 25 °C for 12 h. The reaction mixture was quenched by addition H_2O (50 mL) at 0 °C, and then extracted with EtOAc (25 mL * 3). The combined organic layers were washed with brine (30 mL), filtered and concentrated under reduced pressure to get the product 2-(trichloromethyl)-7-(trifluoromethoxy)-1H-benzimidazole (720 mg, crude) was obtained as a yellow solid. MS (ESI) *m/z* 320.8 $[M+H]^+$

Step 2: methyl 7-(trifluoromethoxy)-1H-benzo[d]imidazole-2-carboxylate

[0001032] To a solution of 2-(trichloromethyl)-7-(trifluoromethoxy)-1H-benzimidazole (720 mg, 2.25 mmol, 1 eq) in MeOH (10 mL) was added Na_2CO_3 (238.85 mg, 2.25 mmol, 1 eq), and the mixture was stirred at 70 °C for 14 h. 1N HCl was added to the solution and the reaction was stirred for 0.5 h. The mixture was extracted with EtOAc (30 mL * 3), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to get the product methyl 7-(trifluoromethoxy)-1H-benzimidazole-2-carboxylate (520 mg, crude) was obtained as a yellow solid. MS (ESI) *m/z* 260.8 $[M+H]^+$

Step 3: 7-(trifluoromethoxy)-1H-benzo[d]imidazole-2-carboxylic acid

[0001033] To a solution of methyl 7-(trifluoromethoxy)-1H-benzimidazole-2-carboxylate (300 mg, 1.15 mmol, 1 eq) in THF (6 mL) and H_2O (2 mL) was added LiOH (165.69 mg,

6.92 mmol, 6 eq), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 2%-40%, 9min) to get the product 7-(trifluoromethoxy)-1H-benzimidazole-2-carboxylic acid (150 mg, 591.12 umol, 51.26% yield, 97% purity) as a white solid. MS (ESI) *m/z* 245.1 $[M-H]^+$

[0001034] ^1H NMR (DMSO-d_6, 400 MHz): δ ppm 7.46 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.10 - 7.14 (m, 1H)

Step 4: (S)-methyl 2-((S)-2-amino-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[0001035] To a solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 625.81 umol, 1 eq) in EtOAc (0.5 mL) was added drop-wise HCl/EtOAc (4 M, 10 mL, 63.92 eq), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to get the product methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, crude, HCl) as a white solid.

Step 5: (S)-methyl 2-((S)-4-methyl-2-(4-(trifluoromethoxy)-1H-benzo[d]imidazole-2-carboxamido)pentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001036] To a solution of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 595.55 umol, 1.22 eq, HCl) and 7-(trifluoromethoxy)-1H-benzimidazole-2-carboxylic acid (120 mg, 487.52 umol, 1 eq) in DMF (1 mL) and DCM (6 mL) was added drop-wise Et_3N (295.99 mg, 2.93 mmol, 407.14 uL, 6.0 eq) and T_3P (930.72 mg, 1.46 mmol, 869.83 uL, 50% purity, 3.0 eq). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (40 mL) at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 0/1) to get the product methyl (2S)-2-[[(2S)-4-methyl-2-[[7-(trifluoromethoxy)-1H-benzimidazole-2-carbonyl]amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (180 mg,

307.11 umol, 62.99% yield, 90% purity) was obtained as a colorless oil. MS (ESI) *m/z* 528.2 $[M+H]^+$.

[0001037] ^{1}H NMR (400 MHz, METHANOL-d_4): δ ppm 7.58 (br d, J = 7.9 Hz, 1H), 7.40 (br t, J = 8.0 Hz, 1H), 7.21 - 7.33 (m, 1H), 4.64 (br t, J = 6.9 Hz, 1H), 4.55 - 4.59 (m, 1H), 3.72 (s, 3H), 3.22 - 3.30 (m, 2H), 2.60 (br d, J = 9.0 Hz, 1H), 2.27 - 2.37 (m, 1H), 2.15 - 2.24 (m, 1H), 1.72 - 1.92 (m, 5H), 1.02 (br dd, J = 12.8, 6.1 Hz, 6H)

Step 6: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)-4-(trifluoromethoxy)-1H-benzo[d]imidazole-2-carboxamide

[0001038] A solution of methyl (2S)-2-[[(2S)-4-methyl-2-[[7-(trifluoromethoxy)-1H-benzimidazole-2-carbonyl]amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (170 mg, 322.28 umol, 1 eq) in ammonia (7 M, 17 mL, 369.24 eq) was stirred at 80 °C for 12 h.

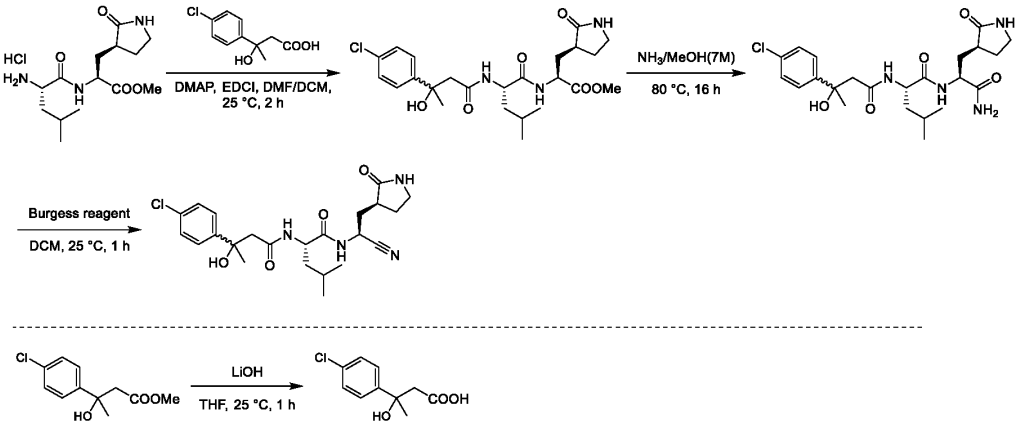
[0001039] The reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-7-(trifluoromethoxy)-1H-benzimidazole-2-carboxamide (150 mg, crude) was obtained as a white solid. MS (ESI) *m/z* 513.2 $[M+H]^+$.

Step 7: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-4-methyl-1-oxopentan-2-yl)-4-(trifluoromethoxy)-1H-benzo[d]imidazole-2-carboxamide

[0001040] To a solution of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-7-(trifluoromethoxy)-1H-benzimidazole-2-carboxamide (100 mg, 195.13 umol, 1 eq) in DCM (6 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (232.51 mg, 975.65 umol, 5.0 eq). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 * 30 mm *3 um; mobile phase: [water (0.2% FA)-ACN]; B%: 30%-70%, 8 min) to get the product N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-7-(trifluoromethoxy)-1H-benzimidazole-2-carboxamide (35.5 mg, 70.86 umol, 36.32% yield, 98.7% purity) was obtained as a white solid. MS (ESI) *m/z* 495.1 $[M+H]^+$.

[00001041] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.73 (s, 1H), 8.86 - 9.04 (m, 2H), 7.71 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.37 - 7.44 (m, 1H), 7.26 - 7.37 (m, 1H), 4.98 (dd, J = 6.9, 1.2 Hz, 1H), 4.54 (br s, 1H), 3.07-3.19 (m, 2H), 2.33 - 2.43 (m, 1H), 2.14 (br dd, J = 8.8, 4.9 Hz, 2H), 1.55 - 1.90 (m, 5H), 0.92 (dd, J = 8.8, 6.2 Hz, 6H)

Example 117. Synthesis of viral protease inhibitor compound 365



Step 1: methyl (2S)-2-[[(2S)-2-[[3-(4-chlorophenyl)-3-hydroxy-butanoyl]amino]-4-methyl -penta noyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[00001042] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin- 3-yl]propanoate;hydro chloride (315.00 mg, 937.99 umol, 1 *eq*) and 3-(4-chlorophenyl)-3-hydroxy- butanoic acid (201.33 mg, 937.99 umol, 1 *eq*) in DCM (3 mL) and DMF (6 mL) was added EDCI (359.62 mg, 1.88 mmol, 2 *eq*) and DMAP (229.19 mg, 1.88 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 h. Upon the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC to get the compound methyl (2S)-2-[[(2S)-2-[[3-(4-chlorophenyl)-3-hydroxy-butanoyl]amino]-4-methyl -penta noyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (90 mg, 172.38 umol, 18.38% yield, 95% purity) and methyl (2S)-2-[[(2S)-2-[[3-(4-chlorophenyl)-3-hydroxy-butanoyl]amino]-4-methyl-pentaneyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (120 mg, 229.84 umol, 24.50% yield, 95% purity) as white solid. MS (ESI) *m/z* 496.3 $[M+H]^+$

[00001043] column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH4HCO3)-ACN];B%: 25%-55%,10min.

Step 2: 3-(4-chlorophenyl)-3-hydroxy-butanoic acid

[0001044] To a mixture of ethyl 3-(4-chlorophenyl)-3-hydroxy-butanoate (500 mg, 2.06 mmol, 1 eq) in H_2O (3 mL) and THF (6 mL) was added $LiOH.H_2O$ (172.90 mg, 4.12 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon the reaction was completed. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate 60 mL (30 mL * 2). The combined organic layers were washed with brine 930 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue compound 3-(4-chlorophenyl)-3-hydroxy-butanoic acid (400 mg, 1.68 mmol, 81.41% yield, 90% purity) as a white solid.

Step 3: (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-[[3-(4-chloro phenyl)-3- hydroxy-butanoyl]amino]-4-methyl-pentanamide

[0001045] To a mixture of methyl (2S)-2-[[(2S)-2-[[3-(4-chlorophenyl)-3-hydroxy-butanoyl]amino]-4-methyl -pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (80 mg, 153.23 umol, 95% purity, 1 *eq*) was added NH_3/MeOH(7M) (7 M, 9.50 mL, 434.00 *eq*). The mixture was stirred at 80 °C for 16 h, and then the reaction mixture was concentrated under reduced pressure to give a residue compound (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] -2-[[3-(4-chlorophenyl)-3-hydroxy-butanoyl]amino]-4-methyl-pentanamide (70 mg, 130.98 umol, 85.48% yield, 90% purity) as a yellow oil. MS (ESI) *m/z* 481.2 $[M+H]^+$.

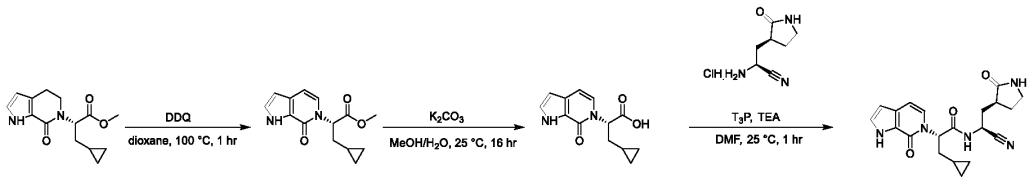
Step 3:(2S)-2-[[3-(4-chlorophenyl)-3-hydroxy-butanoyl]amino]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrro lidin-3-yl]ethyl]-4-methyl-pentanamide

[0001046] To a mixture of (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2- [[3-(4-chlorophenyl)-3-hydroxy-butanoyl]amino]-4-methyl-pentanamide (70 mg, 145.54 umol, 1 eq) in DCM (4 mL) was added Burgess reagent (69.36 mg, 291.07 umol, 2 eq). After stirring the mixture at 25 °C for 60 min, the reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 2). The combined organic layers were concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC to get the compound (2S)-2-[[3-(4-chlorophenyl)-3-hydroxy-butanoyl]amino]-N-[(1S)-1-cyano-2-[(3S)-2- oxopyrrolidin-3-yl]ethyl]-4-methyl-pentanamide (11 mg, 23.76 umol, 16.33% yield, 100% purity) as a white solid. MS (ESI) *m/z* 463.2 $[M+H]^+$

[0001047] Isomer 1: 1H NMR (400MHz, METHANOL-*d*4) δ = 7.51 - 7.42 (m, 2H), 7.36 - 7.26 (m, 2H), 4.96 (dd, *J*=6.0, 10.1 Hz, 1H), 4.27 - 4.17 (m, 1H), 3.30 - 3.23 (m, 2H), 2.83 - 2.63 (m, 2H), 2.51 (dq, *J* =5.3, 9.3 Hz, 1H), 2.34 - 2.17 (m, 2H), 1.94 - 1.72 (m, 2H), 1.57 (s, 3H), 1.54 - 1.26 (m, 3H), 0.93 - 0.77 (m, 6H)

[0001048] Isomer 2: 1H NMR (400MHz, METHANOL-*d*4) δ = 7.44 (d, *J*=8.6 Hz, 2H), 7.34 - 7.24 (m, 2H), 5.06 - 4.93 (m, 1H), 4.26 - 4.13 (m, 1H), 3.38 - 3.32 (m, 1H), 3.29 - 3.24 (m, 1H), 2.85 - 2.62 (m, 2H), 2.53 (dq, *J* =5.5, 9.3 Hz, 1H), 2.42 - 2.17 (m, 2H), 1.98 - 1.74 (m, 2H), 1.52 (s, 3H), 1.49 - 1.36 (m, 2H), 1.31 - 1.18 (m, 1H), 0.90 - 0.79 (m, 3H), 0.72 (d, *J* =6.5 Hz, 3H)

Example 118. Synthesis of viral protease inhibitor compound 265



Step 1: Methyl (2S)-3-cyclopropyl-2-(7-oxo-1H-pyrrolo[2,3-c]pyridin-6-yl)propanoate

[0001049] To a solution of methyl (2*S*)-3-cyclopropyl-2-(7-oxo-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanoate (20 mg, 76.2 umol, 1 *eq*) in dioxane (2 mL) was added DDQ (51.9 mg, 0.22 mmol, 3 *eq*) and the mixture was stirred at 100 °C for 1 hr under microwave. The reaction mixture was concentrated in vacuum. The residue was diluted with ethyl acetate (30 mL), washed with 10% aq. NaOH (10 mL), brine (10 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by *prep*-TLC (petroleum ether/ethyl acetate = 1/1). methyl (2*S*)-3-cyclopropyl-2-(7-oxo-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanoate (10 mg, 38 umol, 50% yield, 100% purity) was obtained as a yellow oil.

[0001050] LCMS: Rt = 0.746 min; for $C_{14}H_{16}N_2O_3$ MS Calcd.: 260.12; MS Found: 260.9 [$M+H^+$].

[0001051] ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (br s, 1H), 7.29 (t, *J* = 2.76 Hz, 1H), 6.98 (d, *J* = 7.03 Hz,1H), 6.64 (d, *J* = 7.03 Hz, 1H), 6.39 (t, *J* = 2.38 Hz, 1H), 5.61 (dd, *J* =

9.79, 5.52 Hz, 1H), 3.74 (s, 3H), 2.17 - 2.07 (m, 1H), 2.06 -1.99 (m, 1H), 0.71 - 0.55 (m, 1H), 0.49 - 0.32 (m, 2H), 0.18 - 0.10 (m, 1H), 0.05 - 0.00 (m, 1H).

Step 2: (2S)-3-cyclopropyl-2-(7-oxo-1H-pyrrolo[2,3-c]pyridin-6-yl)propanoic acid

[0001052] To a solution of methyl (2*S*)-3-cyclopropyl-2-(7-oxo-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanoate (10 mg, 38.4 umol, 1 *eq*) in MeOH (0.5 mL) was added K_2CO_3 (15.9 mg, 0.115 mmol, 3 *eq*) in H_2O (0.2 mL) and the mixture was stirred at 25 °C for 16 hr. After the reaction mixture was concentrated in vacuum, the residue was diluted with H_2O (5 mL), adjusted pH to about 4 with 1M aq. HCl and extracted with ethyl acetate (5 mL*3). The combined organic phase was washed with brine (5 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was used for the next step directly. (2*S*)-3-cyclopropyl-2-(7-oxo-1*H*-pyrrolo[2,3-c]pyridin-6-yl)propanoic acid (8 mg, 32.1 umol, 83.7% yield, 99% purity) was obtained as a white solid.

[0001053] LCMS： Rt = 0.701 min; for $C_{13}H_{14}N_2O_3$ MS Calcd.: 246.10; MS Found: 246.9 [$M+H^+$].

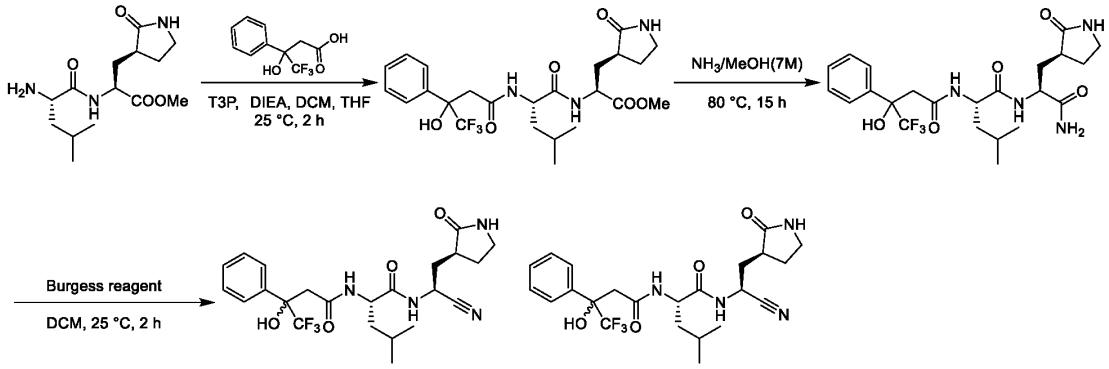
265: N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(7-oxo-1H-pyrrolo[2,3-c]pyridin-6-yl)propanamide

[0001054] To a solution of (2*S*)-3-cyclopropyl-2-(7-oxo-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanoic acid (8 mg, 32.4 umol, 1 *eq*) and (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanenitrile (4.9 mg, 26.2 umol, HCl) in DMF (1 mL) was added TEA (3.2 mg, 32.4 umol, 4 uL, 1 *eq*) and T_3P (31.0 mg, 48.7 umol, 28 uL, 50% purity, 1.5 *eq*). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated in vacuum. The crude product was checked by HPLC and purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40mm*3um; mobile phase: [water(0.05%NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 14%-44%, 9.5min). *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(7-oxo-1*H*-pyrrolo[2,3-*c*]pyridin-6-yl)propanamide (2.9 mg, 23.5% yield) was obtained as a white solid.

[0001055] LCMS： Rt = 0.702 min; for $C_{20}H_{23}N_5O_3$ MS Calcd.: 381.18; MS Found: 382.0 [$M+H^+$].

[0001056] ^{1}H NMR (400 MHz, CD_3OD) δ 7.21 - 7.15 (m, 1H), 7.11 - 7.02 (m, 1H), 6.60 - 6.49 (m,1H), 6.28 - 6.19 (m, 1H), 5.55 - 5.35 (m, 1H), 4.95 - 4.78 (m, 1H), 3.12 - 2.94 (m, 2H), 2.39 - 2.27 (m, 1H), 2.16 -1.99 (m, 2H), 1.90 - 1.82 (m, 2H), 1.76 - 1.61 (m, 2H), 0.56 - 0.43 (m, 1H), 0.31 - 0.17 (m, 2H), 0.04 - 0.02 (m, 1H), 0.02 - 0.00 (m, 1H).

Example 118a. Synthesis of viral protease inhibitor compound 369



Step 1: (2S)-methyl 2-((2S)-4-methyl-2-(4,4,4-trifluoro-3-hydroxy-3-phenylbutanamido)pentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

To a solution of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (140 mg, 467.66 umol, 1 eq) 4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoic acid (164.27 mg, 701.48 umol, 1.5 eq) in DCM (1.5 mL) THF (1.5 mL) was added T_3P (446.40 mg, 701.48 umol, 417.19 uL, 50% purity, 1.5 eq) and DIEA (181.32 mg, 1.40 mmol, 244.37 uL, 3 eq). The mixture was stirred at 25 °C for 2 h. LCMS showed the reaction was complected, and desired MS was observed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residure was purified by neutral *prep*-HPLC to get the product methyl (2S)-2-[[(2S)-4-methyl-2-[(4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoyl)amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (120 mg, 232.77 umol, 49.77% yield) was obtained as white solid. MS (ESI) *m/z* 516.2 $[M+H]^+$.

Step 2: (2S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-methyl-2-(4,4,4-trifluoro-3-hydroxy-3-phenylbutanamido)pentanamide

[0001057] To a solution of methyl (2S)-2-[[(2S)-4-methyl-2-[(4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoyl)amino]pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (120 mg, 232.77 umol, 1 eq) in $MeOH/NH_3$ (7 M, 5 mL, 150.36 eq) The mixture was stirred at

80 °C for 15 h. LCMS showed the reaction was complected, and desired MS was observed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue to get the product (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3R)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methyl-2-[(4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoyl)amino]pentanamide (120 mg, crude) was obtained as colorless oil. MS (ESI) *m/z* 501.2 $[M+H]^+$.

Step 3:

(2S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-4-methyl-2-(4,4,4-trifluoro-3-hydroxy-3-phenylbutanamido)pentanamide

[0001058] To a solution of (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methyl-2-[(4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoyl)amino]pentanamide (120 mg, 239.76 umol, 1 eq) in DCM (3 mL) was added Burgess reagent (114.27 mg, 479.51 umol, 2 eq). The mixture was stirred at 25 °C for 1 h. LCMS showed the reaction was complected, and desired MS was observed. The reaction mixture was quenched by addition H_2O 5 mL, and then extracted with DCM (2.5 mL * 3). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residure was purified by neutral *prep*-HPLC to get the product (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-2-[(4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoyl)amino]pentanamide (20.18 mg, 38.77 umol, 16.17% yield, 92.698% purity) was obtained as white solid. MS (ESI) *m/z* 483.3$[M+H]^+$.

Prep-HPLC condition:

[0001059] column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-55%,8min

[0001060] column: Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 40%-65%,8min

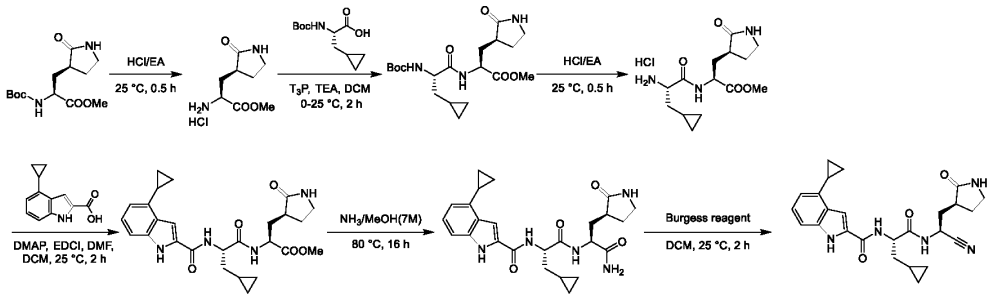
[0001061] ^1H NMR (400 MHz, DMSO-d6) δ ppm 8.83 (d, J=7.72 Hz, 1 H) 8.37 (d, J=8.16 Hz, 1 H) 7.72 (s, 1 H) 7.53 (br d, J=7.06 Hz, 2 H) 7.29 - 7.42 (m, 3 H) 7.16 (s, 1 H) 4.77 -

4.99 (m, 1 H) 4.15 - 4.28 (m, 1 H) 3.03 - 3.20 (m, 4 H) 2.16 - 2.27 (m, 1 H) 1.95 - 2.09 (m, 2 H) 1.57 - 1.78 (m, 2 H) 1.29 - 1.44 (m, 3 H) 0.69 - 0.88 (m, 6 H).

[0001062] (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-2-[(4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoyl)amino]pentanamide (13.28 mg, 27.20 umol, 11.34% yield, 98.809% purity) was obtained as white solid MS (ESI) m/z 483.3[M+H]+.

[0001063] ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.86 (d, J=7.94 Hz, 1 H) 8.58 (d, J=8.16 Hz, 1 H) 7.73 (s, 1 H) 7.51 - 7.62 (m, 2 H) 7.31 - 7.42 (m, 3 H) 6.92 (s, 1 H) 4.86 - 4.96 (m, 1 H) 4.11 (ddd, J=9.65, 8.32, 5.18 Hz, 1 H) 3.29 (br d, J=14.55 Hz, 1 H) 3.06 - 3.20 (m, 2 H) 2.89 (d, J=14.55 Hz, 1 H) 2.21 - 2.36 (m, 1 H) 2.02 - 2.17 (m, 2 H) 1.62 - 1.82 (m, 2 H) 1.20 - 1.38 (m, 2 H) 1.02 - 1.14 (m, 1 H) 0.73 (d, J=6.62 Hz, 3 H) 0.49 (d, J=6.39 Hz, 3 H).

Example 119. Synthesis of viral protease inhibitor compound 375



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001064] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.2 g, 4.19 mmol, 1 *eq*) in HCl/MeOH (10 mL) was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure to crude methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (770 mg, 4.14 mmol, 98.67% yield) as a yellow oil.

Step 2: methyl(2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2- oxopyrrolidin-3-yl]propanoate

[0001065] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (750 mg, 4.03 mmol, 1 *eq*) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-

propanoic acid (923.45 mg, 4.03 mmol, 1 *eq*) in DCM (3 mL) was added TEA (2.04 g, 20.14 mmol, 2.80 mL, 5 *eq*) in one portion at 0 °C. The mixture was added with T_3P (3.84 g, 12.08 mmol, 3.59 mL, 3 *eq*) at 0 °C and stirred at 25 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine 10 mL (10 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.5 g, 3.77 mmol, 93.70% yield) as a yellow oil. MS (ESI) *m/z* 398.3 $[M+H]^+$

Step 3: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propanoate

[0001066] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.3 g, 3.27 mmol, 1 *eq*) in HCl/MeOH (10 mL) was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure to give crude methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (900 mg, 3.03 mmol, 92.54% yield) as a yellow oil.

Step 4: methyl(2S)-2-[[(2S)-3-cyclopropyl-2-[(4-cyclopropyl-1H-indole-2-carbonyl)amino]propanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001067] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (448 mg, 1.51 mmol, 1 *eq*) and 4-cyclopropyl-1H-indole-2-carboxylic acid (364.61 mg, 1.81 mmol, 1.2 *eq*) in DCM (8 mL) was added DMF (2 mL) and EDCI (868.40 mg, 4.53 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added with DMAP (553.43 mg, 4.53 mmol, 3 *eq*) and the reaction was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=5/1 to 0/1) to afford methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-cyclopropyl-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.04 mmol, 68.90% yield) as a white solid. MS (ESI) *m/z* 481.2 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclo propylmethyl)-2-oxo-ethyl]-4-cyclopropyl-1H-indole-2-carboxamide

[0001068] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-cyclopropyl-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.04 mmol, 1 *eq*) in NH_3/MeOH (7M) (7 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1 -(cyclopropylmethyl)-2-oxo-ethyl]-4-cyclopropyl-1H-indole-2-carboxamide (390 mg, 837.73 umol, 80.52% yield) as a white solid. MS (ESI) *m/z* 466.3 $[M+H]^+$

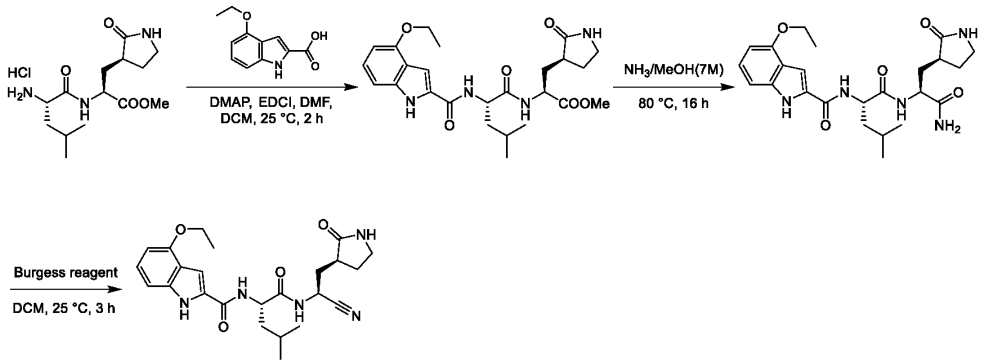
Step 6: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2 -oxo-ethyl]-4-cyclopropyl-1H-indole-2-carboxamide

[0001069] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-cyclopropyl-1H-indole-2-carboxamide (390 mg, 837.73 umol, 1 *eq*) in DCM (7 mL) was added Burgess reagent (1.20 g, 5.03 mmol, 6 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-cyclopropyl-1H-indole-2-carboxamide (68 mg, 151.95 umol, 18.14% yield) as a white solid. MS (ESI) *m/z* 448.3 $[M+H]^+$

[0001070] Column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-55%,8min

[0001071] ^1H NMR (400MHz, DMSO-d_6) δ = 11.55 (s, 1H), 9.12 - 8.84 (m, 1H), 8.59 (d, *J*=7.6 Hz, 1H), 7.84 - 7.65 (m, 1H), 7.48 (d, *J*=1.3 Hz, 1H), 7.21 (d, *J*=8.2 Hz, 1H), 7.06 (t, *J*=7.7 Hz, 1H), 6.64 (d, *J*=7.2 Hz, 1H), 5.09 - 4.87 (m, 1H), 4.69 - 4.36 (m, 1H), 3.20 - 3.06 (m, 2H), 2.46 - 2.07 (m, 4H), 1.95 - 1.39 (m, 4H), 1.01 (br dd, *J*=2.2, 8.3 Hz, 2H), 0.92 - 0.74 (m, 3H), 0.55 - 0.34 (m, 2H), 0.28 - 0.00 (m, 2H)

Example 120. Synthesis of viral protease inhibitor compound 377



Step 1: methyl (2S)-2-[[(2S)-2-[(4-ethoxy -1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino] -3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001072] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin -3-yl]propanoate;hydrochloride (250.00 mg, 671.53 umol, 1 eq, HCl) and 4-ethoxy-1H-indole-2- carboxylicacid (165.36 mg, 805.83 umol, 1.2 eq) in DCM (10 mL) and DMF (5 mL) was added EDCI (257.46 mg, 1.34 mmol, 2 eq) and DMAP (164.08 mg, 1.34 mmol, 2 eq). After stirring the mixture at 25 °C for 2 h, the reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (60 mL, which was extracted as 30 mL * 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether:ethyl acetate = 0:1) to afford methyl(2S)-2-[[(2S)-2-[(4-ethoxy -1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 369.94 umol, 55.09% yield, 90% purity) as a yellow oil.

Step 2: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2- oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3- methyl-butyl]-4-ethoxy-1H-indole-2-carboxamide

[0001073] A mixture of methyl (2S)-2-[[(2S)-2-[(4-ethoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3- [(3S)-2-oxopyrrolidin-3-yl]propanoate (120 mg, 246.63 umol, 1 eq) was added NH_3/MeOH(7M) (4.20 mg, 246.63 umol, 20 mL, 1 eq) was stirred at 80 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue and used next directly. Compound N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2- oxopyrrolidin -3-yl]methyl] ethyl]carbamoyl]-3-methyl-butyl]-4-ethoxy-1H-indole-2-carboxamide (112 mg, 213.76 umol, 86.67% yield, 90% purity) was obtained as a yellow oil.

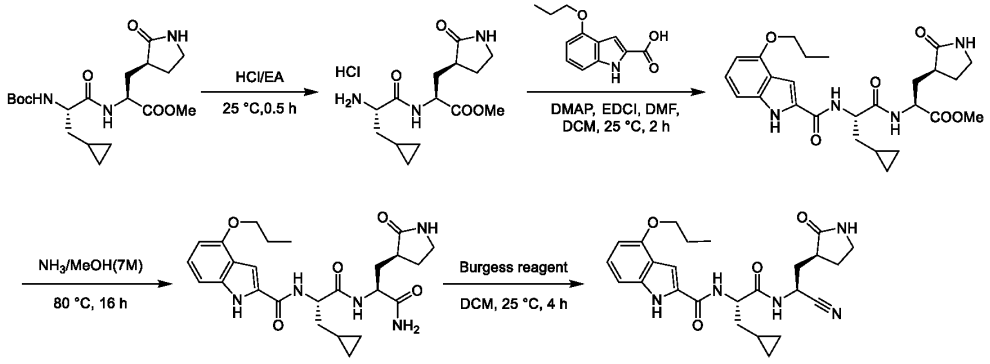
Step 3: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4- ethoxy-1H-indole-2-carboxamide

[0001074] To a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamoyl]-3-methyl-butyl]-4-ethoxy-1H-indole-2-carboxamide (111.11 mg, 212.07 umol, 90% purity, 1 eq) in DCM (2 mL) was added Burgess reagent (151.61 mg, 636.20 umol, 3 eq). After the mixture was stirred at 25 °C for 3 h, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by HCl prep-HPLC to get the compound N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl] carbamoyl]-3-methyl-butyl]-4-ethoxy-1H-indole-2-carboxamide (38 mg, 81.87 umol, 38.61% yield, 97.716% purity) as a white solid. MS (ESI) *m/z* 454.2 $[M+H]^+$

[0001075] Column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water(10 mM NH4HCO3)-ACN]; B%: 30%-60%, 10 min

[0001076] H NMR (400 MHz, DMSO-*d*6) δ = 11.56 (br s, 1H), 8.90 (d, *J*=8.1 Hz, 1H), 8.52 (br d, *J*=7.6 Hz, 1H), 7.72 (s, 1H), 7.39 (s, 1H), 7.11 - 7.03 (m, 1H), 7.01 - 6.96 (m, 1H), 6.48 (d, *J*=7.6 Hz, 1H), 5.04 - 4.92 (m, 1H), 4.57 - 4.37 (m, 1H), 4.14 (q, *J*=7.0 Hz, 2H), 3.21 - 3.03 (m, 2H), 2.43 - 2.28 (m, 1H), 2.21 - 2.04 (m, 2H), 1.82 - 1.46 (m, 5H), 1.41 (t, *J*=7.0 Hz, 3H), 0.91 (dd, *J*=6.4, 19.5 Hz, 6H)

Example 121. Synthesis of viral protease inhibitor compound 379



Step 1: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001077] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.3 g, 3.27 mmol, 1 *eq*) in HCl/MeOH (10 mL) was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (900 mg, 3.03 mmol, 92.54% yield) as a yellow oil.

Step 2: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-propoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001078] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (448 mg, 1.51 mmol, 1 *eq*) and 4-propoxy-1H-indole-2-carboxylic acid (396.37 mg, 1.81 mmol, 1.2 *eq*) in DMF (2 mL) was added DCM (8 mL) and EDCI (866.48 mg, 4.52 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added with DMAP (552.19 mg, 4.52 mmol, 3 *eq*), and the reaction was stirred at 25 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (30 mL, which extracted added as 10 mL * 3). The combined organic layers were washed with brine (10 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by column chromatography (SiO2, petroleum ether/ethyl acetate=5/1 to 0/1) to afford methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-propoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (480 mg, 962.75 umol, 63.90% yield) as a white solid. MS (ESI) *m/z* 499.2 $[M+H]^+$

*Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamid*e

[0001079] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-propoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (480 mg, 962.75 umol, 1 *eq*) in NH_3/MeOH (7M) (3 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give the crude N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide (380 mg, 785.84 umol, 81.62% yield) as a white solid. MS (ESI) *m/z* 484.3 $[M+H]^+$

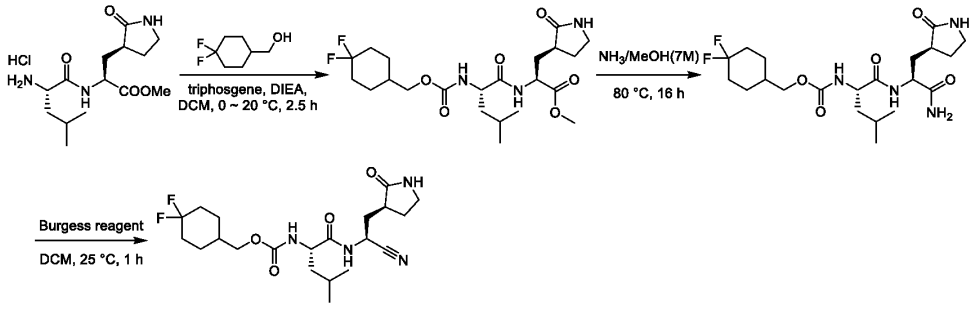
Step 4: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide

[0001080] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide (380 mg, 785.84 umol, 1 *eq*) in DCM (7 mL) was added Burgess reagent (1.12 g, 4.72 mmol, 6 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (neutral condition) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-propoxy-1H-indole-2-carboxamide (120 mg, 257.76 umol, 32.80% yield) was obtained as a white solid. MS (ESI) *m/z* 466.3 $[M+H]^+$

[0001081] Column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-60%,8 min

[0001082] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.55 (br d, *J*=1.7 Hz, 1H), 9.07 - 8.85 (m, 1H), 8.57 (d, *J*=7.6 Hz, 1H), 7.83 - 7.61 (m, 1H), 7.39 (d, *J*=1.6 Hz, 1H), 7.14 - 6.90 (m, 2H), 6.48 (d, *J*=7.6 Hz, 1H), 5.09 - 4.86 (m, 1H), 4.60 - 4.28 (m, 1H), 4.04 (t, *J*=6.4 Hz, 2H), 3.22 - 3.01 (m, 2H), 2.45 - 2.03 (m, 3H), 1.94 - 1.59 (m, 5H), 1.58 - 1.34 (m, 1H), 1.06 (t, *J*=7.4 Hz, 3H), 0.95 - 0.69 (m, 1H), 0.55 - 0.30 (m, 2H), 0.28 - -0.02 (m, 2H)

Example 122. Synthesis of viral protease inhibitor compound 383



Step 1: methyl (2S)-2-[[(2S)-2-[(4,4-difluorocyclohexyl)methoxycarbonylamino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001083] To a mixture of bis(trichloromethyl) carbonate (940 mg, 3.17 mmol, 1.36 eq) in THF (2 mL) was added DIEA (602.47 mg, 4.66 mmol, 811.95 uL, 2 eq) at 25 °C, and

then (4,4-difluorocyclohexyl)methanol (350 mg, 2.33 mmol, 1 eq) in THF (2 mL) was added at 0 °C. After stirring the mixture at 0 °C for 15 min, the reaction was heated to 25 °C and stirred for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue (4,4-difluorocyclohexyl)methyl carbonochloridate (400 mg, 1.51 mmol, 64.57% yield, 80% purity) as a yellow oil.

[0001084] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin -3-yl]propanoate;hydrochloride (300 mg, 893.32 umol, 1 eq) in THF (3 mL) was added DIEA (346.37 mg, 2.68 mmol, 466.80 uL, 3 eq) and (4,4-difluorocyclohexyl)methyl carbonochloridate (356.14 mg, 1.34 mmol, 80% purity, 1.5 eq) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=8/1 to 0/1) to afford methyl (2S)-2- [[(2S)-2-[(4,4-difluorocyclohexyl)methoxycarbonylamino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (320 mg, 605.65 umol, 67.80% yield, 90% purity) as a yellow oil. MS (ESI) *m/z* 476 $[M+H]^+$

Step 2: 4,4-difluorocyclohexyl)methyl N-[(1S)-1-[[(1S)-2- amino-2-oxo-1-[[(3S)-2-oxopyrrolidin -3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]carbamate

[0001085] To a mixture of methyl (2S)-2-[[(2S)-2-[(4,4-difluorocyclohexyl)methoxycarbonylamino]-4-methyl- pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 630.88 umol, 1 eq) was added NH_3/MeOH(7M) (10.74 mg, 630.89 umol, 1 eq). After stirring the mixture at 80 °C for 16 h, the reaction mixture was concentrated under reduced pressure to give a residue and used next step directly. Compound (4,4-difluorocyclohexyl)methyl N-[(1S)-1-[[(1S)-2- amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]carbamate (280 mg, 364.81 umol, 57.83% yield, 60% purity) was obtained as a yellow oil. MS (ESI) *m/z* 461.3 $[M+H]^+$

Step 3: (4,4-difluorocyclohexyl)methyl N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl] ethyl]carbamoyl]-3-methyl-butyl]carbamate

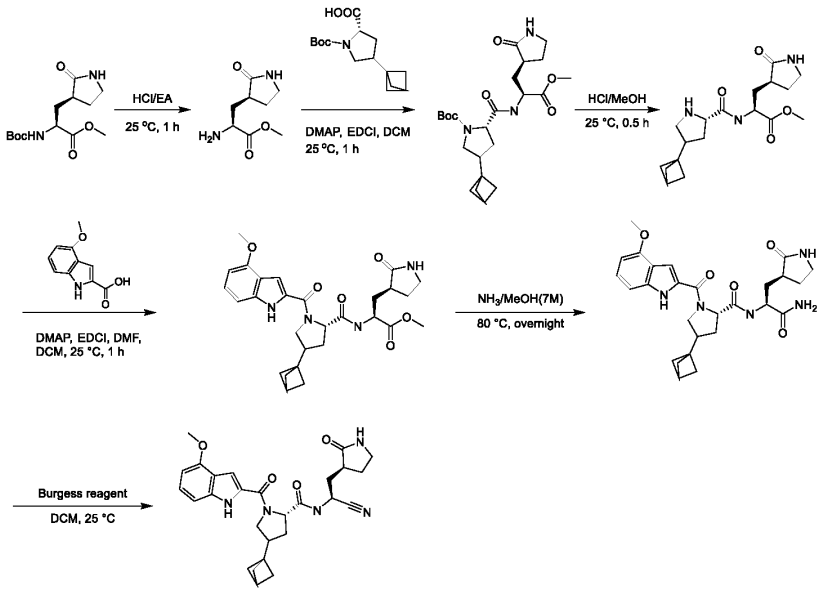
[0001086] To a mixture of (4,4-difluorocyclohexyl)methylN-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopy rrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]carbamate

(230 mg, 299.67 umol, 60% purity, 1 eq) in DCM (6 mL) was added Burgess reagent (142.83 mg, 599.33 umol, 2 eq). The mixture was stirred at 25 °C for 60 min. Upon completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (20 mL). The combined organic layers concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC to get the compound (4,4-difluorocyclohexyl)methyl N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl] ethyl]carbamoyl]-3-methyl-butyl]carbamate (48 mg, 100.77 umol, 33.63% yield, 92.9% purity) as a white solid. MS (ESI) m/z 443.3 [M+H]+

Column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water(10 mM NH4HCO3)-ACN]; B%: 25%-45%,8 min

H NMR (400 MHz, DMSO-d6) δ = 8.81 (d, J=8.0 Hz, 1H), 7.81 - 7.66 (m, 1H), 7.40 (br d, J=7.8 Hz, 1H), 5.01 - 4.81 (m, 1H), 4.03 - 3.88 (m, 1H), 3.83 (br d, J=6.1 Hz, 2H), 3.21 - 3.03 (m, 2H), 2.40 - 2.22 (m, 1H), 2.18 - 1.94 (m, 4H), 1.90 - 1.54 (m, 8H), 1.53 - 1.30 (m, 2H), 1.29 - 1.10 (m, 2H), 0.87 (dd, J=6.5, 12.8 Hz, 6H)

Example 123. Synthesis of viral protease inhibitor compound 385



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001087] A solution of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (350 mg, 1.22 mmol, 1 *eq*) in HCl/EtOAc (4 M, 5 mL,

16.36 *eq*) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated to give methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (272 mg, crude, HCl) as a yellow oil.

Step 2:

(2S)-tert-butyl 4-(bicyclo[1.1.1]pentan-1-yl)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate

[0001088] To a solution of methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (272 mg, 1.22 mmol, 1 *eq*, HCl) in DCM (6 mL) was added DMAP (298.47 mg, 2.44 mmol, 2 *eq*) and EDCI (468.34 mg, 2.44 mmol, 2 *eq*), and then (2*S*)-4-(1-bicyclo[1.1.1]pentanyl)-1-*tert*-butoxycarbonyl-pyrrolidine-2-carboxylic acid (343.68 mg, 1.22 mmol, 1 *eq*) was added. The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O (20 mL) at 25 °C, and then extracted with DCM (25 mL * 3). The combined organic layers were washed with brine (25 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 0/1) to give *tert*-butyl (2*S*)-4-(1-bicyclo[1.1.1]pentanyl)-2-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]pyrrolidine-1-carboxylate (450 mg, 1.00 mmol, 81.95% yield) as a yellow solid. MS (ESI) *m/z 450.1* $[M+H]^+$

Step 3:

(2S)-methyl 2-((2S)-4-(bicyclo[1.1.1]pentan-1-yl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001089] A solution of *tert*-butyl (2*S*)-4-(1-bicyclo[1.1.1]pentanyl)-2-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]pyrrolidine-1-carboxylate (350 mg, 778.58 umol, 1 *eq*) in HCl/MeOH (5 mL) was stirred at 25 °C for 0.5 h. Upon completion, the reaction mixture was concentrated to give methyl (2*S*)-2-[[(2*S*)-4-(1-bicyclo[1.1.1]pentanyl)pyrrolidine-2-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (300 mg, crude, HCl) as a yellow solid.

Step 4:

(2S)-methyl 2-((2S)-4-(bicyclo[1.1.1]pentan-1-yl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001090] To a solution of 4-methoxy-1*H*-indole-2-carboxylic acid (222.95 mg, 1.17 mmol, 1.5 *eq*), methyl (2*S*)-2-[[(2*S*)-4-(1-bicyclo[1.1.1]pentanyl)pyrrolidine-2-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 777.43 umol, 1 *eq*, HCl) in DCM (6 mL) was added DMAP (284.94 mg, 2.33 mmol, 3 *eq*) and CDI (378.18 mg, 2.33 mmol, 3 *eq*). The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was poured into H_2O (20 mL) at 25 °C, and then extracted with DCM (30 mL *3). The combined organic layers were washed with brine (25 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: Kromasil C18 (250 * 50 mm * 10 um);mobile phase: [water(10 mM $HCOONH_4$)-ACN]; B%: 35%-55%, 10 min) to give methyl (2*S*)-2-[[(2*S*)-4-(1-bicyclo[1.1.1]pentanyl)-1-(4-methoxy-1*H*-indole-2-carbonyl)pyrrolidine-2-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 373.91 umol, 48.09% yield, 97.70% purity) and methyl (2*S*)-2-[[(2*S*)-4-(1-bicyclo[1.1.1]pentanyl)-1-(4-methoxy-1*H*-indole-2-carbonyl)pyrrolidine-2-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (70 mg, 127.20 umol, 16.36% yield, 94.96% purity) as a yellow solid. MS (ESI) *m/z 523.2* $[M+H]^+$

Step 5: (2S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(bicyclo[1.1.1]pentan-1-yl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[0001091] Isomer 1: A solution of methyl (2S)-2-[[(2S)-4-(1-bicyclo[1.1.1]pentanyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 382.71 umol, 1 *eq*) in NH_3/MeOH (7 M, 8 mL, 146.33 *eq*) was stirred at 80 °C for 24 h. Upon completion, the reaction mixture was concentrated to give (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-(1-bicyclo[1.1.1]pentanyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (150 mg, crude) as a yellow solid. MS (ESI) *m/z 508.2* $[M+H]^+$

[0001092] Isomer 2: A solution of methyl (2S)-2-[[(2S)-4-(1-bicyclo[1.1.1]pentanyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (70 mg, 133.95 umol, 1 *eq*) in NH_3/MeOH (7 M, 4 mL, 209.04 *eq*) was stirred at 80 °C for 24 hr. Upon completion, the reaction mixture was concentrated to give (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-(1-

bicyclo[1.1.1]pentanyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (50 mg, crude) as a yellow solid. MS (ESI) *m/z 508.2* $[M+H]^+$

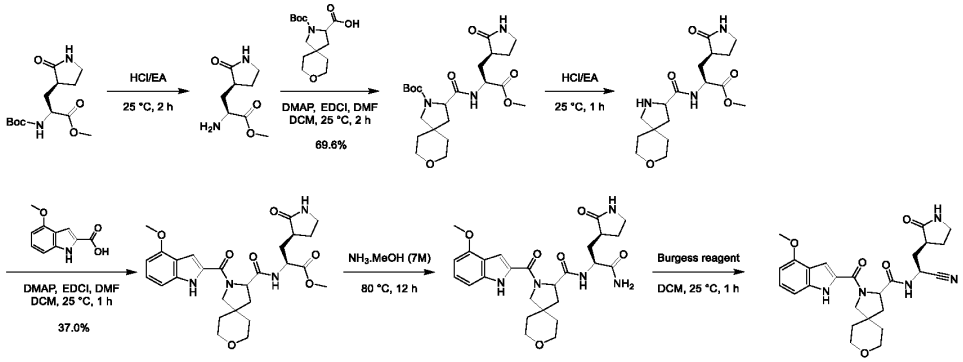
Step 6: (2S)-4-(bicyclo[1.1.1]pentan-1-yl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[0001093] Isomer 1: To a solution of (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-(1-bicyclo[1.1.1]pentanyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (145 mg, 285.67 umol, 1 *eq*) in DCM (4 mL) was added Burgess reagent (680.76 mg, 2.86 mmol, 10 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O (20 mL) at 25 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 * 30 mm * 3 um; mobile phase: [water(10 mM NH4HCO3)-ACN];B%: 30%-50%,8 min) to give (2S)-4-(1-bicyclo[1.1.1]pentanyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (46 mg, 93.11 umol, 32.59% yield, 99.09% purity) as a white solid. MS (ESI) *m/z 490.2* $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d_4) δ = 7.24 - 6.79 (m, 3H), 6.56 - 6.41 (m, 1H), 5.05 (s, 1H), 4.63 (d, *J*=4.4 Hz, 1H), 4.34 - 3.36 (m, 6H), 3.03 - 1.50 (m, 15H), 1.37 (d, *J*=8.4 Hz, 1H).

[0001094] Isomer 2: To a solution of (2S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-(1-bicyclo[1.1.1]pentanyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (50 mg, 98.51 umol, 1 *eq*) in DCM (2 mL) was added Burgess reagent (70.42 mg, 295.52 umol, 3 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O (20 mL) at 25 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(10 mM NH4HCO3)-ACN];B%: 30%-50%,8 min) to give (2S)-4-(1-bicyclo[1.1.1]pentanyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (10 mg, 20.14 umol, 20.45% yield, 98.61% purity) as a white solid. MS (ESI) m/z 490.2

$[M+H]^+$; ^1H NMR (400 MHz, MeOD-d_4) δ = 7.16 (d, J=7.9 Hz, 1H), 7.10 - 7.00 (m, 2H), 6.53 (d, J=7.7 Hz, 1H), 5.01 (s, 1H), 4.66 (d, J=5.4, 8.3 Hz, 1H), 4.18 - 4.05 (m, 1H), 3.95 (s, 3H), 3.89 (s, 1H), 3.79 (d, J=6.4, 9.9 Hz, 1H), 2.70 - 2.60 (m, 1H), 2.51 (d, J=17.0 Hz, 2H), 2.43 (d, J=4.3, 8.5, 12.5 Hz, 1H), 2.30 (d, J=6.6, 13.7 Hz, 1H), 2.20 - 2.11 (m, 1H), 2.04 - 1.83 (m, 3H), 1.81 - 1.69 (m, 7H).

Example 124. Synthesis of viral protease inhibitor compound 387



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001095] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.3 g, 1.05 mmol, 1 *eq*) in HCl/EtOAc (4 M, 5 mL, 19.09 *eq*) was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.2 g, crude) as a yellow gum.

Step 2: tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-8-oxa-2-azaspiro[4.5]decane-2-carboxylate

[0001096] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.18 g, 808.38 umol, 1 *eq*, HCl) in DMF (1 mL) and DCM (2 mL) was added DMAP (197.52 mg, 1.62 mmol, 2 *eq*), 2-tert-butoxycarbonyl-8-oxa-2-azaspiro[4.5]decane-3-carboxylic acid (230.66 mg, 808.38 umol, 1 *eq*) and EDCI (309.93 mg, 1.62 mmol, 2 *eq*), and then the resulting solution was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with DCM (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 1:1 to 0:1) to give tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-

[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (0.3 g, 562.26 umol, 69.55% yield, 85% purity) as a colorless oil. MS (ESI) *m/z* 454.2 $[M+H]^+$.

Step 3: (2S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-(8-oxa-2-azaspiro[4.5]decane-3-carboxamido)propanoate

[0001097] A mixture of tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-8-oxa-2-azaspiro[4.5]decane-2-carboxylate (0.25 g, 551.23 umol, 1 *eq*) in HCl/EtOAc (5 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-(8-oxa-2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.2 g, crude, HCl) as a yellow oil.

Step 4: (2S)-methyl 2-(2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001098] To a solution of methyl (2S)-2-(8-oxa-2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.2 g, 512.99 umol, 1 *eq*, HCl) in DMF (1 mL) and DCM (2 mL) was added DMAP (125.34 mg, 1.03 mmol, 2 *eq*), and then 4-methoxy-1H-indole-2-carboxylic acid (107.88 mg, 564.29 umol, 1.1 *eq*) and EDCI (196.68 mg, 1.03 mmol, 2 *eq*) was added. The solution was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (5 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1 to DCM:MeOH = 10:1) to give methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.13 g, 232.06 umol, 45.24% yield, 94% purity) as a yellow solid. MS (ESI) *m/z* 527.2 $[M+H]^+$.

Step 5: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carboxamide

[0001099] A mixture of methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.13 g, 246.88 umol, 1 *eq*) in NH_3.MeOH (7 M, 3 mL, 85.06 *eq*) was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give

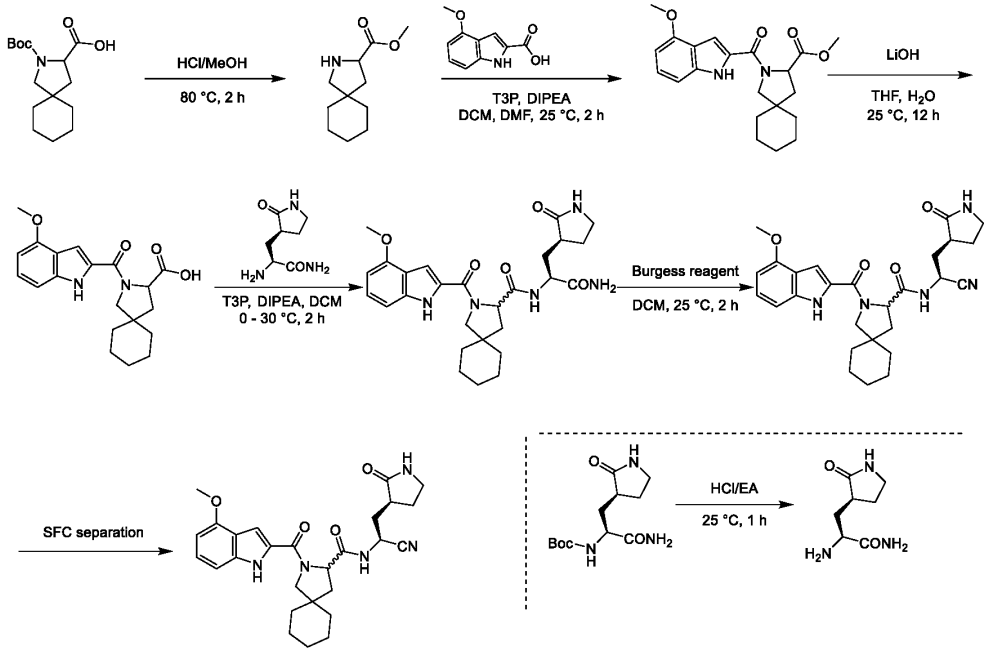
N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carboxamide (0.12 g, crude) as a yellow oil. MS (ESI) *m/z* 512.2 $[M+H]^+$.

Step 6: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carboxamide

[0001100] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carboxamide (0.12 g, 234.57 umol, 1 *eq*) in DCM (2 mL) was added Burgess reagent (167.70 mg, 703.72 umol, 3 *eq*), and then the solution was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 15%-45%,10 min) to give N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carboxamide (44.25 mg, 88.76 umol, 37.84% yield, 99% purity) as a white solid. MS (ESI) *m/z* 494.2 $[M+H]^+$.

[0001101] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.23 - 7.08 (m, 2H), 7.08 - 6.98 (m, 1H), 6.53 (br d, *J* = 7.6 Hz, 1H), 5.02 (br dd, *J* = 5.7, 10.1 Hz, 1H), 4.72 - 4.62 (m, 2H), 4.19 - 4.03 (m, 1H), 3.98 - 3.81 (m, 4H), 3.77 - 3.62 (m, 4H), 3.29 - 3.17 (m, 1H), 2.52 - 2.20 (m, 3H), 2.02 - 1.42 (m, 8H).

Example 125. Synthesis of viral protease inhibitor compound 389



Step 1: (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide

[0001102] A solution of *tert*-butyl *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamate (2 g, 7.37 mmol, 1 eq) in HCl/EtOAc (4 M, 50 mL, 27.13 eq) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (1.2 g, crude) as a white solid.

Step 2: methyl 2-azaspiro[4.5]decane-3-carboxylate

[0001103] A solution of 2-*tert*-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (3 g, 10.59 mmol, 1 eq) was added in HCl/MeOH (4 M, 50 mL, 18.89 eq) was stirred at 80 °C for 2 h. The mixture was concentrated under the reduced pressure affording the product methyl 2-azaspiro[4.5]decane-3-carboxylate (2 g, crude) as a yellow oil.

Step 3: methyl 2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate

[0001104] To a solution of methyl 2-azaspiro[4.5]decane-3-carboxylate (2 g, 10.14 mmol, 1 eq) and 4-methoxy-1*H*-indole-2-carboxylic acid (2.33 g, 12.17 mmol, 1.2 eq) in DCM (30 mL) and DMF (5 mL) was added T3P (12.90 g, 20.28 mmol, 12.06 mL, 50% purity, 2 eq) and DIEA (3.93 g, 30.41 mmol, 5.30 mL, 3 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (100 mL), and

extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 10:1 to 0:1) affording the product methyl 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate (3 g, 8.10 mmol, 79.88% yield) as a white solid. MS (ESI) *m/z* 371.1 $[M+H]^+$

Step 4: 2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid

[0001105] To a solution of methyl 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate (3 g, 8.10 mmol, 1 eq) in THF (45 mL) and H_2O (15 mL) was added $LiOH.H_2O$ (1.70 g, 40.49 mmol, 5 eq). The mixture was stirred at 25 °C for 12 h. Upon completion, the mixture was quenched by addition H_2O (50 mL), and then added aq. HCl (1 M) to adjust the pH to about 3 - 4, and then extracted with ethyl acetate (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure affording the product 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (2.6 g, crude) as a white solid. MS (ESI) *m/z* 357.1 $[M+H]^+$

Step 5: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001106] To a solution of 2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (1 g, 2.81 mmol, 1 eq) and (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (720.49 mg, 4.21 mmol, 1.5 eq) in DCM (30 mL) was added T_3P (3.57 g, 5.61 mmol, 3.34 mL, 50% purity, 2 eq) and DIEA (1.09 g, 8.42 mmol, 1.47 mL, 3 eq) at 0 °C. The mixture was stirred at 30 °C for 1 h. Upon completion, the mixture was quenched by addition H_2O (100 mL), and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1:0 to 10:1) affording the product *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (700 mg, 1.37 mmol, 48.96% yield) as a white solid. MS (ESI) *m/z* 510.3 $[M+H]^+$

Step 6: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001107] To a solution of *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (700 mg, 1.37 mmol, 1 eq) in DCM (10 mL) was added Burgess reagent (982.03 mg, 4.12 mmol, 3 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Kromasil C18 (250 * 50 mm * 10 um); mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 10 min) affording the product *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (500 mg, 1.02 mmol, 74.05% yield) as a white solid. MS (ESI) *m/z* 492.3 $[M+H]^+$

Step 7: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

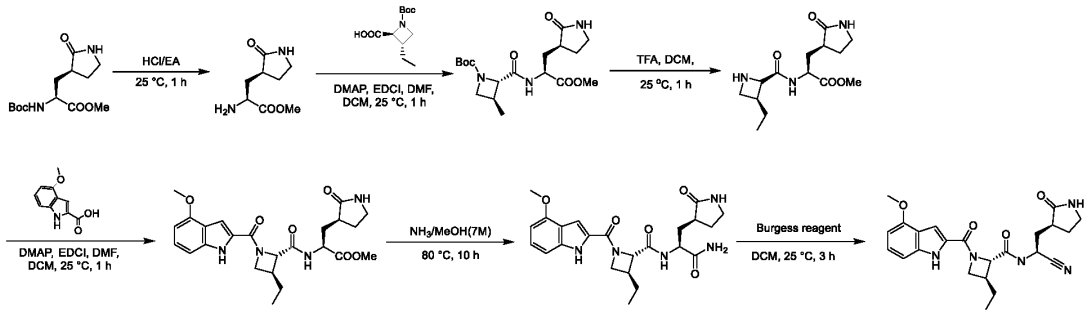
[0001108] *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (500 mg, 1.02 mmol) was separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O IPA]; B%: 55% - 55%, 9 min) affording the product *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (264 mg, 537.04 umol, 52.80% yield, 100% purity) as a white solid. MS (ESI) *m/z* 492.3 $[M+H]^+$

[0001109] ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.28 - 6.76 (m, 3H), 6.60 - 6.38 (m, 1H), 5.05 (br dd, *J* = 5.2, 10.2 Hz, 1H), 4.63 – 4.60 (m, 1H), 4.03 - 3.85 (m, 5H), 3.74 - 3.28 (m, 1H), 2.73 (br dd, *J* = 5.0, 8.6 Hz, 1H), 2.51 - 2.28 (m, 2H), 2.27 - 2.08 (m, 1H), 1.96 - 1.72 (m, 2H), 1.69 - 1.38 (m, 11H), 1.37 - 1.09 (m, 1H).

[0001110] *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 2 (140 mg, 284.51 umol, 27.97% yield, 99.9% purity) as a white solid. MS (ESI) *m/z* 492.3 $[M+H]^+$

[0001111] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.30 - 6.81 (m, 3H), 6.53 (br d, J = 2.0 Hz, 1H), 5.12 - 4.95 (m, 2H), 4.70 - 4.55 (m, 2H), 4.08 - 3.86 (m, 4H), 3.84 - 3.72 (m, 1H), 2.62 - 2.40 (m, 1H), 2.36 - 2.18 (m, 2H), 1.94 - 1.69 (m, 3H), 1.68 - 1.34 (m, 11H).

Example 126. Synthesis of viral protease inhibitor compound 391



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001112] To a solution of methyl (S)-methyl 2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (350 mg, 1.22 mmol, 1 eq) was added HCl/EtOAc (12 mL) and the mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated in the vacuum to give a crude product (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate (330 mg, crude) as yellow oil. MS (ESI) m/z 187.1 $[M+H]^+$

Step 2: (2S,3S)-tert-butyl3-ethyl-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)azetidine-1-carboxylate

[0001113] To a solution of (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate (330 mg, 1.77 mmol, 1 eq), (2S,3S)-1-(tert-butoxycarbonyl)-3-ethylazetidine-2-carboxylic acid (406.32 mg, 1.77 mmol, 1 eq) in DMF (2 mL) and DCM (10 mL) was added EDCI (679.47 mg, 3.54 mmol, 2 eq) and DMAP (433.02 mg, 3.54 mmol, 2 eq). After stirring the mixture at 25 °C for 1 h, the mixture was quenched by addition H_2O (50 mL) and then extracted with EtOAc (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue and was purified by prep-TLC (SiO_2, petroleum ether:ethyl acetate = 0:1) to give the crude product (2S,3S)-tert-butyl 3-ethyl-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)azetidine-1-carboxylate (270 mg, 679.31 umol, 38.33% yield) was obtained as yellow oil. MS (ESI) m/z 398.2 $[M+H]^+$

Step 3: (S)-methyl 2-((2S,3S)-3-ethylazetidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001114] To a solution of (2S,3S)-tert-butyl 3-ethyl-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)azetidine-1-carboxylate (240 mg, 603.83 umol, 1 eq) in DCM (1 mL) was added TFA (4.13 g, 36.23 mmol, 2.68 mL, 60 eq), and the resulting mixture was stirred at 25 °C for 1 h. Upon completion, the residue was poured into $NaHCO_3$ (10 mL) and was extracted with EtOAc (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the crude product (S)-methyl 2-((2S,3S)-3-ethylazetidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (200 mg, crude) as white solid. MS (ESI) m/z 298.2 $[M+H]^+$

Step 4:(S)-methyl2-((2S,3S)-3-ethyl-1-(4-methoxy-1H-indole-2-carbonyl)azetidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001115] To a solution of (S)-methyl 2-((2S,3S)-3-ethylazetidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (200 mg, 672.61 umol, 1 eq), 4-methoxy-1H-indole-2-carboxylic acid (128.59 mg, 672.61 umol, 1 eq) in DCM (1 mL) was added EDCI (257.88 mg, 1.35 mmol, 2 eq), and DMAP (164.34 mg, 1.35 mmol, 2 eq), and the mixture was stirred at 25 °C for 1 h. Upon completion, the residue was poured into H_2O (10 mL) and was extracted with EtOAc (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and was purified by prep-TLC (SiO_2, [etroleum ether:ethyl acetate = 0:1) to give product (S)-methyl 2-((2S,3S)-3-ethyl-1-(4-methoxy-1H-indole-2-carbonyl)azetidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (90 mg, 191.28 umol, 28.44% yield) as white solid. MS (ESI) m/z 471.2 $[M+H]^+$

Step5:(2S,3S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-3-ethyl-1-(4-methoxy-1H-indole-2-carbonyl)azetidine-2-carboxamide

[0001116] A solution of (S)-methyl 2-((2S,3S)-3-ethyl-1-(4-methoxy-1H-indole-2-carbonyl)azetidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (80 mg, 170.03 umol, 1 eq) in NH_3/MeOH (7 M, 16.00 mL, 658.72 eq) was stirred at 80 °C for 16 h. Upon completion, the mixture was concentrated in the vacuum to give product (2S,3S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-3-ethyl-1-(4-methoxy-

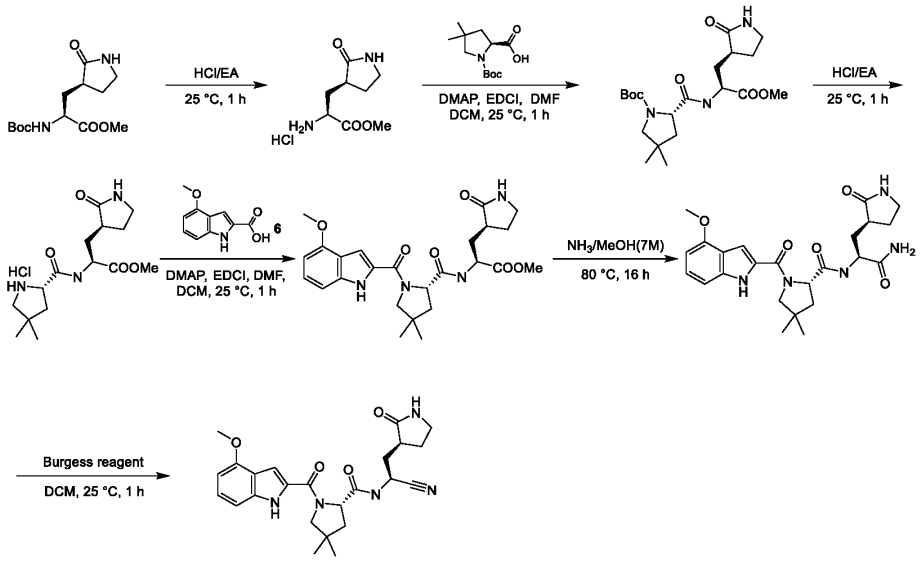
1H-indole-2-carbonyl)azetidine-2-carboxamide (66 mg, crude) as a white solid. MS (ESI) m/z 456.2 $[M+H]^+$

Step6:(2S,3S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-3-ethyl-1-(4-methoxy-1H-indole-2-carbonyl)azetidine-2-carboxamide

[0001117] To a solution of (2S,3S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-3-ethyl-1-(4-methoxy-1H-indole-2-carbonyl)azetidine-2-carboxamide (66 mg, 144.89 umol, 1 eq) in DCM (3 mL) was added Burgess reagent (414.35 mg, 1.74 mmol, 12 eq), and then the mixture was stirred at 25 °C for 3 h. Upon completion, the mixture was concentrated in the vacuum and was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 15%-45%,8 min) to give (2S,3S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-3-ethyl-1-(4-methoxy-1H-indole-2-carbonyl)azetidine-2-carboxamide (5 mg, 11.43 umol, 7.89% yield). MS (ESI) m/z 438.2 $[M+H]^+$

[0001118] ^1H NMR (400 MHz, MeOD-d_4) δ = 7.24 - 7.11 (m, 1H), 7.09 - 6.61 (m, 2H), 6.52 - 6.51 (m, 1H), 5.08 - 4.87 (m, 0.5H), 4.75-4.73 (m, 1.5H), 4.56 - 4.43 (m, 1H), 4.42 - 4.00 (m, 1H), 3.93 (s, 3H), 3.22 - 2.90 (m, 1H), 2.65 - 2.63 (m, 2H), 2.42 - 2.07 (m, 2H), 2.04 - 1.49 (m, 5H), 1.01 – 0.99 (m, 3H)

Example 127. Synthesis of viral protease inhibitor compound 395



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride

[0001119] To methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 1.05 mmol, 1 *eq*) was added HCl/EtOAc (4 M, 30 mL) at 25 °C, and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate;hydrochloride (230 mg, crude) as a yellow oil and used directly for next step.

Step 2:

(S)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4,4-dimethylpyrrolidine-1-carboxylate

[0001120] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (230 mg, 1.03 mmol, 1 *eq*, HCl), (2S)-1-tert-butoxycarbonyl-4,4-dimethyl-pyrrolidine-2-carboxylic acid (251.31 mg, 1.03 mmol, 1 *eq*), DMAP (252.38 mg, 2.07 mmol, 2 *eq*), EDCI (396.02 mg, 2.07 mmol, 2 *eq*), DMF (2 mL) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 0/1) to afford (S)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-

yl)carbamoyl)-4,4-dimethylpyrrolidine-1-carboxylate (200 mg, 486.04 umol, 47.05% yield), as a yellow oil. MS (ESI) *m/z* 412.2 $[M+H]^+$.

Step 3: (S)-methyl-2-((S)-4,4-dimethylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001121] A mixture of (S)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4,4-dimethylpyrrolidine-1-carboxylate (200 mg, 486.04 umol, 1 *eq*) and HCl/EtOAc (4 M, 20 mL) was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a product (S)-methyl-2-((S)-4,4-dimethylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (170 mg, crude, HCl) as a yellow oil and used directly for next step.

Step 4: (S)-methyl 2-((S)-1-(4-methoxy-1H-indole-2-carbonyl)-4,4-dimethylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001122] A mixture of (S)-methyl-2-((S)-4,4-dimethylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (170 mg, 488.74 umol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (93.44 mg, 488.74 umol, 1 *eq*), DMAP (119.42 mg, 977.47 umol, 2 *eq*), EDCI (187.38 mg, 977.47 umol, 2 *eq*), DMF (2 mL) and DCM (4 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 0/1) to get the compound (S)-methyl-2-((S)-1-(4-methoxy-1H-indole-2-carbonyl)-4,4-dimethylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (180 mg, 371.48 umol, 76.01% yield) as yellow solid. MS (ESI) *m/z* 485.2 $[M+H]^+$.

Step 5: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4,4-dimethylpyrrolidine-2-carboxamide

[0001123] A mixture of (S)-methyl-2-((S)-1-(4-methoxy-1H-indole-2-carbonyl)-4,4-dimethylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (180 mg, 371.48 umol, 1 *eq*), and NH_3/MeOH (7 M, 7 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a product (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-

carbonyl)-4,4-dimethylpyrrolidine-2-carboxamide (170 mg, crude) as a yellow solid. MS (ESI) *m/z* 470.2 $[M+H]^+$.

Step 6: (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)-4,4-dimethylpyrrolidine-2-carboxamide

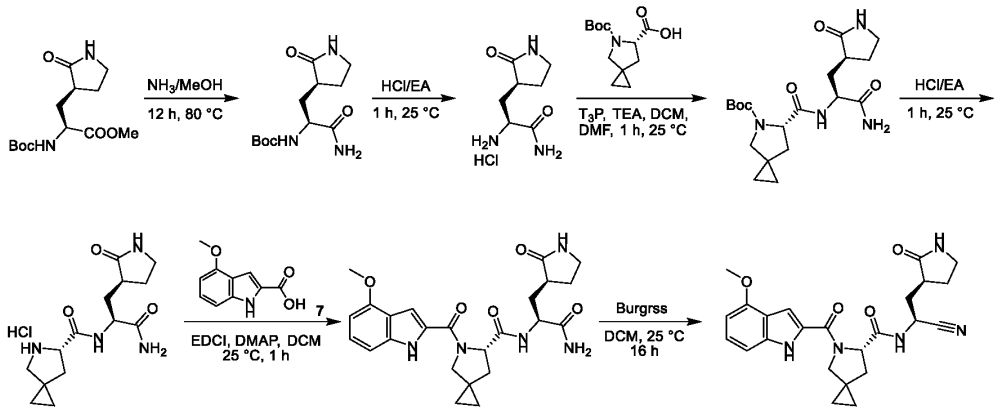
[0001124] A mixture of (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-1-(4-methoxy-1H-indole-2-carbonyl)-4,4-dimethylpyrrolidine-2-carboxamide (160 mg, 340.76 umol, 1 *eq*), Burgess reagent (649.66 mg, 2.73 mmol, 8 *eq*) and DCM (25 mL) was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 15%-40%,8 min) to get the product (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)-4,4-dimethylpyrrolidine-2-carboxamide Isomer 1 (27 mg, 58.95 umol, 17.30% yield, 98.58% purity), as white solid. MS (ESI) *m/z* 452.3 $[M+H]^+$.

[0001125] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.76 - 11.39 (m, 1H), 9.18 - 8.79 (m, 1H), 7.85 - 7.46 (m, 1H), 7.21 - 6.67 (m, 3H), 6.58 - 6.35 (m, 1H), 5.13 - 4.81 (m, 1H), 4.74 - 4.31 (m, 1H), 3.97 - 3.55 (m, 5H), 3.31 - 3.05 (m, 2H), 2.47 - 1.96 (m, 4H), 1.85 - 1.27 (m, 3H), 1.25 - 0.80 (m, 6H).

[0001126] (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)-4,4-dimethylpyrrolidine-2-carboxamide Isomer 2 (3 mg, 6.41 umol, 1.88% yield, 96.44% purity), as white solid. MS (ESI) *m/z* 452.3 $[M+H]^+$.

[0001127] ^1H NMR (400MHz, DMSO- d_6) δ = 11.78 - 11.34 (m, 1H), 9.33 - 8.76 (m, 1H), 7.91 - 7.53 (m, 1H), 7.23 - 6.67 (m, 3H), 6.61 - 6.31 (m, 1H), 5.09 - 4.80 (m, 1H), 4.61 - 4.43 (m, 1H), 4.01 - 3.67 (m, 5H), 3.20 - 2.99 (m, 2H), 2.43 - 1.91 (m, 4H), 1.86 - 1.55 (m, 3H), 1.33 - 0.83 (m, 6H).

Example 128. Synthesis of viral protease inhibitor compound 397



Step 1: tert-butyl N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamate

[0001128] To a solution of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (1 g, 3.49 mmol, 1 *eq*) in NH_3/MeOH (7 M, 15 mL) was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The *tert*-butyl *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamate (900 mg, crude) was obtained as white solid. MS (ESI) *m/z* 272.2 $[M+H]^+$.

Step 2: *(2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide*

[0001129] A solution of tert-butyl *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamate (900 mg, 3.32 mmol, 1 *eq*) in HCl/EA (4 M, 15 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (650 mg, crude, HCl) as white solid. MS (ESI) *m/z* 172.1 $[M+H]^+$.

Step 3: tert-butyl (6S)-6-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-5-azaspiro[2.4]heptane-5-carboxylate

[0001130] A solution of (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (400 mg, 1.93 mmol, 1 *eq*, HCl), (6*S*)-5-*tert*-butoxycarbonyl-5-azaspiro[2.4]heptane-6-carboxylic acid (464.77 mg, 1.93 mmol, 1 *eq*) and TEA (974.58 mg, 9.63 mmol, 1.34 mL, 5 *eq*) was dissolved in DCM (8 mL) and DMF (3 mL), and then the solution cooled to 0 °C. After adding T_3P (3.68 g, 5.78 mmol, 3.44 mL, 50% purity, 3 *eq*) to the solution, the mixture was stirred for 1 h and warmed to 25 °C gradually. Upon completion, the mixture was

added H_2O (50 mL) and then extracted with ethyl acetate (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to get the product tert-butyl (6*S*)-6-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-5-azaspiro[2.4]heptane-5-carboxylate (200 mg, crude) was obtained as yellow solid. MS (ESI) *m/z* 395.2 $[M+H]^+$.

Step 4: (6S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-5-azaspiro[2.4]heptane-6-carboxamide

[0001131] A solution of tert-butyl (6*S*)-6-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-5-azaspiro[2.4]heptane-5-carboxylate (200 mg, 464.12 umol, 1 *eq*, HCl) in HCl/EtOAc (4 M, 15 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to afford (6*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-5-azaspiro[2.4]heptane-6-carboxamide (140 mg, crude, HCl) as a white solid. MS (ESI) *m/z* 295.2 $[M+H]^+$.

Step 5: (6S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-5-(4-methoxy-1H-indole-2-carbonyl)-5-azaspiro[2.4]heptane-6-carboxamide

[0001132] To a solution of (6*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-5-azaspiro[2.4]heptane-6-carboxamide (140 mg, 423.20 umol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (80.91 mg, 423.20 umol, 1 *eq*), EDCI (202.82 mg, 1.06 mmol, 2.5 *eq*) was added DMAP (155.11 mg, 1.27 mmol, 3 *eq*) in DCM (3 mL), and then the reaction was stirred at 25 °C for 1 h. Upon completion, the mixture was added H_2O (30 mL) and then extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford (6S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-5-(4-methoxy-1H-indole-2-carbonyl)-5-azaspiro[2.4]heptane-6-carboxamide (80 mg, 117.37 umol, 27.73% yield, 68.59% purity) as yellow solid. MS (ESI) *m/z* 468.2 $[M+H]^+$.

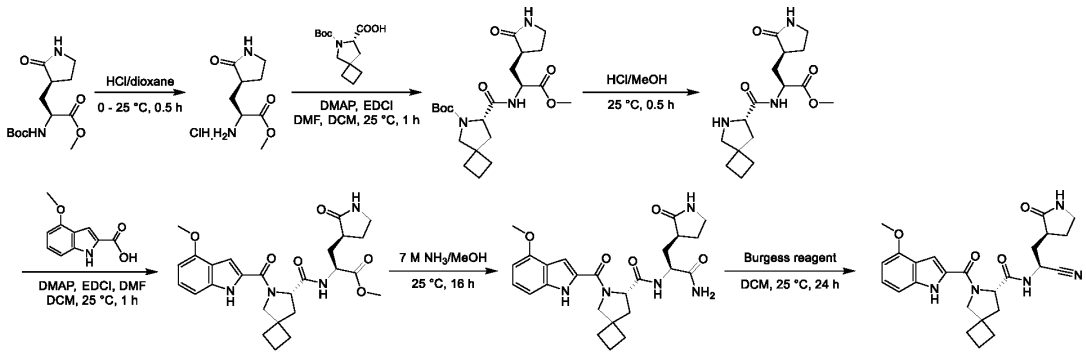
Step 6: (6S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5-(4-methoxy-1H-indole-2-carbonyl)-5-azaspiro[2.4]heptane-6-carboxamide

[0001133] A solution of (6*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-5-(4-methoxy-1*H*-indole-2-carbonyl)-5-azaspiro[2.4]heptane-6-carboxamide (80 mg, 171.12 umol, 1 *eq*) and methoxycarbonyl-

(triethylammonio)sulfonyl-azanide (163.11 mg, 684.47 umol, 4 *eq*) in DCM (5 mL) was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated and concentrated under reduced pressure to afford (6*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-5-(4-methoxy-1H-indole-2-carbonyl)-5-azaspiro[2.4]heptane-6-carboxamide (15.5 mg, 34.44 umol, 20.13% yield, 99.88% purity) as a white solid. MS (ESI) *m/z* 450.2 $[M+H]^+$.

[0001134] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.23 - 7.12 (m, 1H), 6.87 - 7.10(m, 2H), 6.59 - 6.39 (m, 1H), 5.35 - 5.07 (m, 2H), 4.85 - 4.69 (m, 1H), 4.10 - 3.61 (m, 5H), 3.03 - 2.17 (m, 4H), 2.13 - 1.62 (m, 3H), 1.62 - 1.22 (m, 1H), 0.87 - 0.57 (m, 4H).

Example 129. Synthesis of viral protease inhibitor compound 399



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[0001135] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (130 mg, 454.03 umol, 1 eq) in HCl/dioxane (4 M, 2.27 mL, 20 eq) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (173.4 mg, 451.67 umol, 99.48% yield, 58% purity, HCl) as a yellow liquid.

Step 2: (S)-tert-butyl 7-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-6-azaspiro[3.4]octane-6-carboxylate

[0001136] To a solution of (7S)-6-tert-butoxycarbonyl-6-azaspiro[3.4]octane-7-carboxylic acid (105.34 mg, 412.59 umol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (158.4 mg, 412.59 umol, 58% purity, 1 eq, HCl) in DCM (1.2 mL) and DMF (0.4 mL) was added DMAP (100.81 mg, 825.19 umol, 2 eq) and EDCI (158.19 mg,

825.19 umol, 2 eq). After stirring the mixture at 25 °C for 1 h, the residue was diluted with H_2O (6 mL) and extracted with ethyl acetate (3 mL). The combined organic layers were washed with ethyl acetate (3 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate =0/1) afford tert-butyl (7S)-7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (66.3 mg, 156.55 umol, 37.94% yield) as a yellow liquid. MS (ESI) *m/z* 424.0 $[M+H]^+$

Step 3: (S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-((S)-6-azaspiro[3.4]octane-7-carboxamido)propanoate

[0001137] A solution of tert-butyl (7S)-7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (66.3 mg, 156.55 umol, 1 eq) in HCl/MeOH (4 M, 782.76 uL, 20 eq) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford methyl (2S)-2-[[(7S)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (71.1 mg, 156.09 umol, 99.71% yield, 79% purity, HCl) as a yellow liquid.

Step 4: (S)-methyl 2-((S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001138] To a solution of methyl (2S)-2-[[(7S)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (62.8 mg, 137.87 umol, 79% purity, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (26.36 mg, 137.87 umol, 1 eq) in DCM (1.2 mL) and DMF (0.4 mL) was added DMAP (33.69 mg, 275.74 umol, 2 eq) and EDCI (52.86 mg, 275.74 umol, 2 eq) at 25 °C for 1 h. The residue was diluted with brine (6 mL) and extracted with EtOAc (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate =0/1) to get the product methyl (2S)-2-[[(7S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (33.2 mg, 66.86 umol, 48.50% yield) was obtained as a white solid. MS (ESI) *m/z* 497.1 $[M+H]^+$

Step 5: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

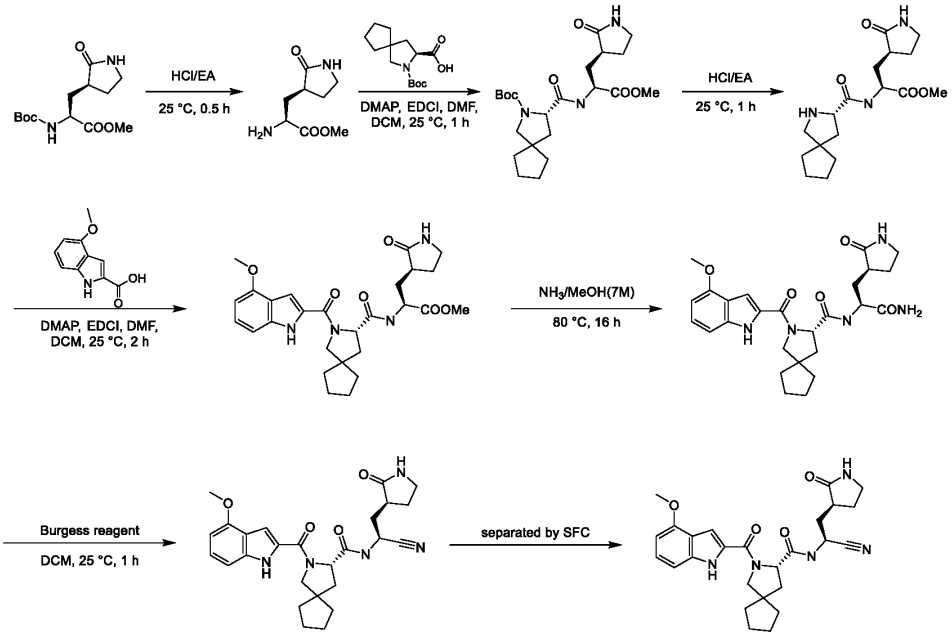
[0001139] A mixture of methyl (2S)-2-[[(7S)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (23.0 mg, 46.32 umol, 1 eq) and ammonia (7 M, 4 mL, 604.50 eq) was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford (7S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (15 mg, crude) as a yellow solid. MS (ESI) *m/z* 482.2 $[M+H]^+$

Step 6: (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[0001140] A solution of (7S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (15 mg, 28.66 umol, 92% purity, 1 eq) and Burgess reagent (13.66 mg, 57.32 umol, 2 eq) was stirred at 25 °C for 24 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30 mm * 10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 20% - 45%, 8 min) to afford (7S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (3.01 mg, 6.49 umol, 22.66% yield, 100% purity) as a white solid. MS (ESI) *m/z* 464.3 $[M+H]^+$

[0001141] ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 6.95 - 7.24 (m, 3 H) 6.47 - 6.58 (m, 1 H) 5.01 (br dd, *J*=10.67, 5.19 Hz, 1 H) 4.58 (t, *J*=7.09 Hz, 1 H) 3.82 - 4.19 (m, 5 H) 3.19 (br t, *J*=8.52 Hz, 1 H) 2.93 - 3.07 (m, 1 H) 2.28 - 2.56 (m, 3 H) 2.16 - 2.27 (m, 2 H) 1.94 - 2.14 (m, 6 H) 1.47 - 1.86 (m, 2 H).

Example 130. Synthesis of viral protease inhibitor compound 401



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001142] methyl (2*S*)-2-(tert-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (400 mg, 1.40 mmol, 1 eq) in HCl/EtOAc (4 M, 10 mL, 28.63 eq) was stirred at 25 °C for 0.5 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (300 mg, crude, HCl) as a yellow solid.

Step 2: (S)-tert-butyl3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.4]nonane-2-carboxylate

[0001143] methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 1.35 mmol, 1 eq, HCl) and (3*S*)-2-tertbutoxycarbonyl-2-azaspiro[4.4]nonane-3-carboxylic acid (362.87 mg, 1.35 mmol, 1 eq) in DMF (2 mL) and DCM (5 mL) was added DMAP (329.19 mg, 2.69 mmol, 2 eq) and EDCI (516.56 mg, 2.69 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (10 mL), and then extracted with DCM (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 5:1 to 0:1) affording the product *tert*-butyl(3*S*)-3-

[[(1*S*)-2-methoxy-2-oxo-1- [[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.4]nonane-2-carboxylate (340 mg, 777.09 umol, 57.68% yield) as a yellow oil.

Step 3: (S)-methyl3-((S)-2-oxopyrrolidin-3-yl)-2-((S)-2-azaspiro[4.4]nonane-3-carboxamido)propanoate

[0001144] *tert*-butyl(3*S*)-3-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.4]nonane-2-carboxylate (340 mg, 777.09 umol, 1 eq) in HCl/EtOAc (4 M, 10 mL, 51.47 eq) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressured affording the product methyl(2*S*)-2-[[(3*S*)-2-azaspiro[4.4]nonane-3-carbonyl]amino] -3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (250 mg, crude, HCl) as a yellow oil.

Step 4: (S)-methyl2-((S)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001145] methyl(2*S*)-2-[[(3*S*)-2-azaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 668.67 umol, 1 eq, HCl) and 4-methoxy-1*H*-indole-2-carboxylic acid (127.84 mg, 668.67 umol, 1 eq) in DMF (2 mL) and DCM (6 mL) was added DMAP (163.38 mg, 1.34 mmol, 2 eq) and EDCI (256.37 mg, 1.34 mmol, 2 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (10 mL), and then extracted with DCM (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, PE:EA = 0:1) affording the product methyl(2*S*)-2-[[(3*S*)-2-(4-methoxy-1*H*-indole-2-carbonyl)-2 -azaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (180 mg, 352.54 umol, 52.72% yield) as a yellow oil. MS (ESI) *m/z* 511.2 $[M+H]^+$

Step 5: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide

[0001146] methyl(2*S*)-2-[[(3*S*)-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (180

mg, 352.54 umol, 1 eq) in ammonia (7 M, 20 mL, 397.12 eq) was stirred as 80 °C for 16 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product (3*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl] methyl]ethyl]-2-(4-methoxy-1*H*-indole-2- carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (170 mg, crude) as a yellow oil.

Step 6: (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide

[0001147] (3*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (170 mg, 343.04 umol, 1 eq) in DCM (3 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (408.74 mg, 1.72 mmol, 5 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5 um; mobile phase: [water(10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 10 min) affording the product (3*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2 -carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (25 mg, 51.09 umol, 14.89% yield, 97.6% purity) as a white solid. MS (ESI) *m/z* 478.2 $[M+H]^+$

[0001148] ^1H NMR (400 MHz, MeOD-d_4) δ = 7.22 - 7.12 (m, 1H), 7.11 - 6.98 (m, 2H), 6.58 - 6.45 (m, 1H), 5.11 - 4.95 (m, 1H), 4.65 - 4.52 (m, 1H), 3.94 (s, 3H), 3.93 - 3.80 (m, 2H), 3.28 - 3.18 (m, 1H), 2.54 - 2.02 (m, 4H), 2.01 - 1.48 (m, 12H).

Step 7: (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide

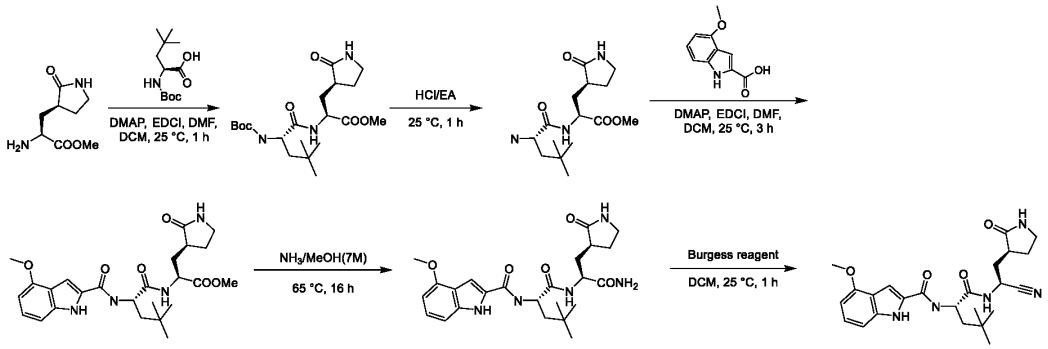
[0001149] Isomer 1: (S)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (30 mg, 62.82 umol) was separated by prep-SFC (column: DAICEL CHIRALPAK IC (250 mm * 30 mm, 5 um); mobile phase: [Neu-ETOH]; B%: 40% - 40%, 15 min) affording the product (3S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1H- indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (12.11 mg, 24.62 umol, 39.20% yield, 97.1% purity) as a white solid. MS (ESI) m/z 478.2 $[M+H]^+$

[0001150] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.20 - 7.11 (m, 1H), 7.08 - 6.85 (m, 2H), 6.59 - 6.42 (m, 1H), 5.05 (br dd, J = 5.6, 10.4 Hz, 1H), 4.58 (br dd, J = 7.4, 9.6 Hz, 1H), 3.97 - 3.92 (m, 3H), 3.88 - 3.52 (m, 2H), 3.28 (br s, 1H), 2.87 - 2.65 (m, 1H), 2.47 - 2.29 (m, 2H), 2.25 - 2.16 (m, 1H), 2.03 - 1.53 (m, 11H), 1.34 - 1.20 (m, 1H).

[0001151] Isomer 2: (*S*)-*N*-((*S*)-1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (30 mg, 62.82 umol) was separated by prep-SFC (column: DAICEL CHIRALPAK IC (250 mm * 30 mm, 5 um); mobile phase: [Neu-ETOH]; B%: 40% - 40%, 15 min) affording the product (3*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*- indole-2-carbonyl)-2-azaspiro[4.4]nonane-3-carboxamide (16.81 mg, 34.46 umol, 54.86% yield, 97.9% purity) as a white solid. MS (ESI) *m/z* 478.2 $[M+H]^+$

[0001152] ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ = 7.23 - 7.13 (m, 1H), 7.10 - 6.84 (m, 2H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.03 (br dd, *J* = 5.7, 10.4 Hz, 1H), 4.67 - 4.54 (m, 1H), 4.00 - 3.57 (m, 5H), 3.27 - 3.16 (m, 1H), 2.55 - 2.39 (m, 1H), 2.37 - 2.04 (m, 3H), 2.02 - 1.44 (m, 11H), 1.43 - 1.16 (m, 1H).

Example 131. Synthesis of viral protease inhibitor compound 405



Step 1: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001153] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (225 mg, 1.21 mmol, 1 *eq*) in DMF (2 mL) and DCM (4 mL) was added TEA (733.62 mg, 7.25 mmol, 1.01 mL, 6 *eq*) and T_3P (1.15 g, 3.62 mmol, 1.08 mL, 3 *eq*) and (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (296.42 mg, 1.21 mmol, 1 *eq*). The solution was stirred for 1 h at 25 °C. The reaction was diluted with H_2O (40 mL) and

extracted with ethyl acetate (50 mL* 3) and the organic layer was cautiously concentrated to give crude Compound methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (440 mg, crude) as a yellow solid used directly for the next step. MS (ESI) *m/z* 414.1 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001154] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (440 mg, 1.06 mmol, 1 *eq*) in HCl/MeOH (10 mL) was stirred for 1 h at 25 °C. TLC (DCM:MeOH = 10:1) showed desired, and the reaction was cautiously concentrated to give crude. Compound methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (310 mg, crude) as a yellow solid used directly for the next step. MS (ESI) *m/z* 314.3 $[M+H]^+$

Step 3: methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001155] To a solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (310 mg, 989.18 umol, 1 eq) in DMF (4 mL) and DCM (4 mL) was added EDCI (379.25 mg, 1.98 mmol, 2 eq) was added DMAP (241.70 mg, 1.98 mmol, 2 eq) and 4-methoxy-1H-indole-2-carboxylic acid (189.11 mg, 989.18 umol, 1 eq). The solution was stirred for 3 h at 25 °C, and then the reaction was diluted with H_2O (40 mL) and extracted with ethyl acetate (80 mL* 3) and the organic layer was cautiously concentrated to give crude. The crude was purified by pre-TLC (SiO_2, EA:MeOH=10:1) to give product. Compound methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 411.05 umol, 41.55% yield) was obtained. MS (ESI) *m/z* 487.2 $[M-H]^+$

Step 4: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[0001156] A solution of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (135 mg, 277.46 umol, 1 *eq*) in NH_3/MeOH (7 M, 8 mL, 201.83 *eq*) was

stirred for 16 h at 65 °C. HPLC showed desired. The reaction was cautiously concentrated to give crude. Compound N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (130 mg, crude) was obtained as a yellow solid used directly for the next step. MS (ESI) *m/z* 472.3 $[M+H]^+$

[0001157] Prep-HPLC condition: column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 35%-55%,8 min

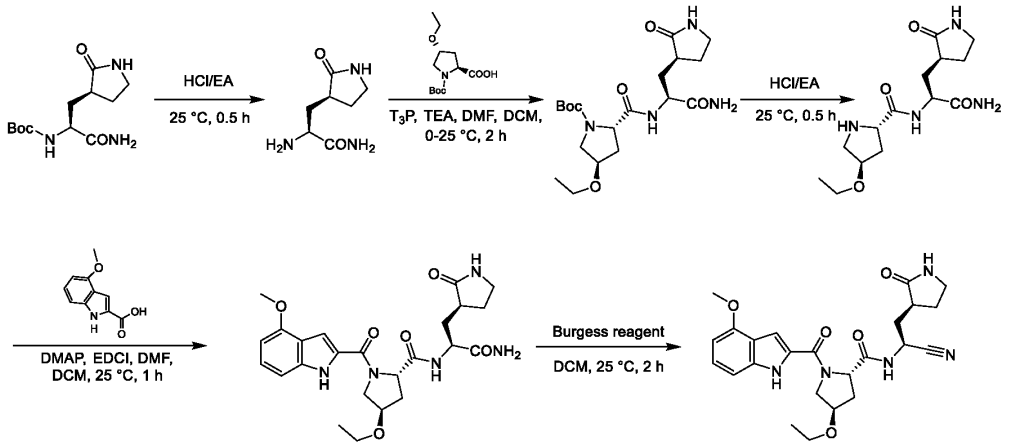
Step 5: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[0001158] To a solution of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (130 mg, 275.69 umol, 1 *eq*) in DCM (7 mL) was added Burgess reagent (197.09 mg, 827.06 umol, 3 *eq*). The solution was stirred for 1 h at 25 °C. The reaction was cautiously concentrated to give crude, and the crude was purified by pre-HPLC(TFA) to give N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (36 mg, 75.41 umol, 27.35% yield, 95% purity) as a white solid. MS (ESI) *m/z* 454.1 $[M+H]^+$.

[0001159] Prep-HPLC condition: column: Phenomenex luna C18 80*40 mm*3 um; mobile phase: [water(0.04% HCl)-ACN];B%: 30%-55%,7 min

[0001160] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 1.02 (s, 9 H) 1.74 - 1.94 (m, 4 H) 2.21 - 2.37 (m, 2 H) 2.52 - 2.63 (m, 1 H) 3.16 - 3.26 (m, 2 H) 3.92 (s, 3 H) 4.63 (dd, *J*=8.49, 4.30 Hz, 1 H) 4.98 - 5.06 (m, 1 H) 6.50 (d, *J*=7.72 Hz, 1 H) 7.02 (d, *J*=8.38 Hz, 1 H) 7.10 - 7.16 (m, 1 H) 7.23 (d, *J*=0.88 Hz, 1 H).

Example 132. Synthesis of viral protease inhibitor compound 409



Step 1: (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide

[0001161] A mixture of *tert*-butyl *N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamate (300 mg, 1.11 mmol, 1 eq) in HCl/EtOAc (4 M, 10 mL, 36.17 eq) was stirred at 25 °C for 0.5 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (200 mg, crude, HCl) as a white solid.

Step 2: (2S,4R)-tert-butyl2-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4-ethoxypyrrolidine-1-carboxylate

[0001162] (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanamide (200 mg, 963.12 umol, 1 eq, HCl) and (2*S*,4*R*)-1-*tert*-butoxycarbonyl-4-ethoxy-pyrrolidine-2-carboxylic acid (249.74 mg, 963.12 umol, 1 eq) in DMF (4 mL) and DCM (8 mL) was added TEA (487.29 mg, 4.82 mmol, 670.27 uL, 5 eq) and T3P (1.84 g, 2.89 mmol, 1.72 mL, 50% purity, 3 eq) at 0 °C. The mixture was stirred at 25 °C for 2 h. Upon completion, the mixture was quenched by addition H_2O (30 mL) and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) affording the product *tert*-butyl (2*S*,4*R*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2- oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-ethoxypyrrolidine-1-carboxylate (140 mg, 339.41 umol, 35.24% yield) as a yellow solid. MS (ESI) *m/z* 413.1 $[M+H]^+$

Step 3: (2S,4R)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-ethoxypyrrolidine-2-carboxamide

[0001163] A mixture of *tert*-butyl(2*S*,4*R*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamoyl]-4-ethoxypyrrolidine-1-carboxylate (100 mg, 242.44 umol, 1 eq) in HCl/EtOAc (4 M, 10 mL, 164.99 eq) was stirred at 25 °C for 0.5 h. Upon completion, the mixture was concentrated under the reduced pressure affording the product (2*S*,4*R*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2- oxopyrrolidin-3-yl]methyl]ethyl]-4-ethoxy-pyrrolidine-2-carboxamide (80 mg, crude, HCl) as a white solid.

Step 4: (2S,4R)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-ethoxy-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[0001164] A mixture of (2*S*,4*R*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-ethoxy -pyrrolidine-2-carboxamide (80 mg, 229.34 umol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (65.77 mg, 344.01 umol, 1.5 eq) in DCM (3 mL) and DMF (1 mL) was added DMAP (56.04 mg, 458.68 umol, 2 eq) and EDCI (87.93 mg, 458.68 umol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was quenched by addition H_2O (30 mL) and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) affording the product (2*S*,4*R*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-ethoxy-1-(4-methoxy-1Hindole-2-carbonyl)pyrrolidine-2-carboxamide (100 mg, crude) as a yellow oil. MS (ESI) *m/z* 486.2 $[M+H]^+$

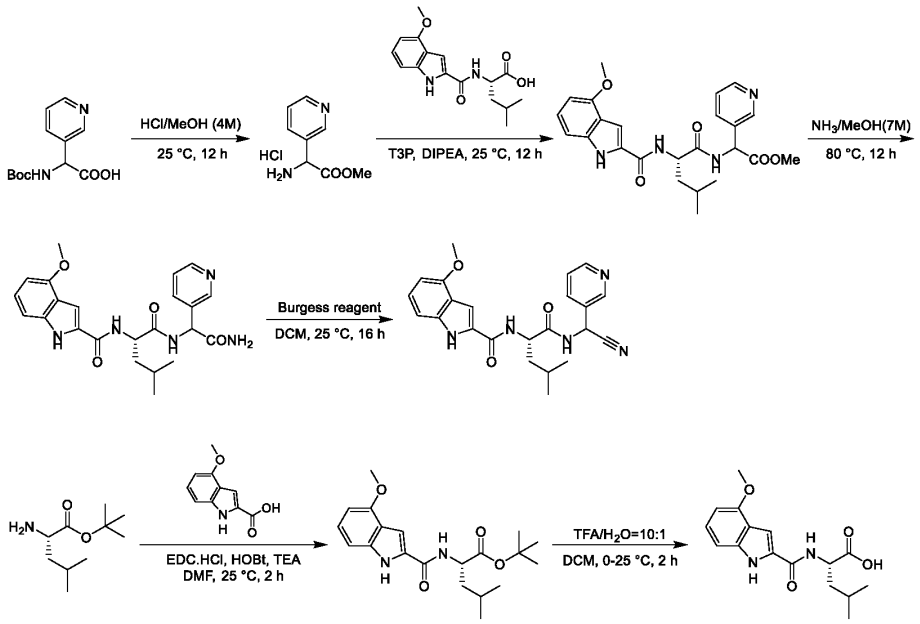
Step 5: (2S,4R)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-4-ethoxy-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[0001165] To a mixture of (2*S*,4*R*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-ethoxy-1-(4-methoxy-1*H*-indole-2-carbonyl)pyrrolidine-2-carboxamide (80 mg, 164.77 umol, 1 eq) in DCM (3 mL) was added Burgess reagent (196.33 mg, 823.84 umol, 5 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 20% - 45%, 10 min) affording the product (2*S*,4*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-4-

ethoxy-1-(4-methoxy-1*H*-indole-2-carbonyl)pyrrolidine-2-carboxamide (28 mg, 58.81 umol, 35.69% yield, 98.2% purity) as a white solid. MS (ESI) *m/z* 468.2 $[M+H]^+$

[0001166] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.19 - 7.13 (m, 1H), 7.09 - 6.86 (m, 2H), 6.57 - 6.42 (m, 1H), 5.17 - 5.01 (m, 1H), 4.69 - 4.58 (m, 1H), 4.36 - 4.18 (m, 1H), 4.16 - 3.97 (m, 2H), 3.96 - 3.85 (m, 3H), 3.68 - 3.44 (m, 2H), 3.00 - 2.54 (m, 2H), 2.50 - 2.31 (m, 2H), 2.25 - 2.02 (m, 2H), 2.01 - 1.72 (m, 2H), 1.69 - 1.26 (m, 1H), 1.25 - 1.13 (m, 3H).

Example 133. Synthesis of viral protease inhibitor compound 433



Step 1: methyl 2-amino-2-(3-pyridyl)acetate

[0001167] To 2-(tert-butoxycarbonylamino)-2-(3-pyridyl)acetic acid (0.5 g, 1.98 mmol, 1 *eq*) was added HCl/MeOH (4 M, 20 mL, 40.36 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to get the crude product. The crude product was used the next step without purification. Methyl 2-amino-2-(3-pyridyl)acetate (400 mg, crude, HCl) was obtained as a yellow oil and used directly next step. MS (ESI) *m/z* 167.1 $[M+H]^+$

Step 2: methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-2- (3-pyridyl)acetate

[0001168] To a mixture of (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (600.76 mg, 1.97 mmol, 1 *eq*) and methyl 2-amino-2-(3-pyridyl)acetate (400 mg, 1.97 mmol, 1 *eq*, HCl), DIPEA (1.28 g, 9.87 mmol, 1.72 mL, 5 *eq*) in THF (1.2 mL) and DCM (1.2 mL) was added T_3P (1.88 g, 2.96 mmol, 1.76 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL * 2) to get the organic phase. The organic phase was concentrated to get the crude product. The residue was purified by pre-HPLC. Methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-2-(3-pyridyl)acetate (0.3 g, crude) was obtained as a white solid. MS (ESI) *m/z* 453.2 $[M+H]^+$

[0001169] Prep-HPLC condition: column: Kromasil C18 (250*50 mm*10 um);mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-50%,10 min.

Step 3: N-[(1S)-1-[[2-amino-2-oxo-1-(3-pyridyl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H- indole-2-carboxamide

[0001170] To a mixture of methyl 2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl] amino]-2-(3-pyridyl)acetate (0.2 g, 441.99 umol, 1 *eq*) was added NH_3/MeOH (7 M, 6 mL, 95.03 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to the 25 °C and concentrated to get the product. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1, R_f = 0.22). N-[(1S)-1-[[2-amino-2-oxo-1-(3-pyridyl)ethyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide (70 mg, crude) was obtained as a light yellow solid. MS (ESI) *m/z* 438.2 $[M+H]^+$

Step 4: N-[(1S)-1-[[cyano(3-pyridyl)methyl]carbamoyl]-3-methyl-butyl]-4-methoxy-1H-indole-2- carboxamide

[0001171] To a mixture of N-[(1S)-1-[[2-amino-2-oxo-1-(3-pyridyl)ethyl]carbamoyl]-3-methyl-butyl]-4- methoxy-1H-indole-2-carboxamide (60 mg, 137.15 umol, 1 *eq*) in DCM (0.2 mL) was added Burgess reagent (65.37 mg, 274.29 umol, 2 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated to get the crude product. The crude product was purified by pre-HPLC twice. N-[(1S)-1-[[cyano(3-pyridyl)methyl]carbamoyl]-3-methyl-butyl] -4-methoxy-1H-

indole-2-carboxamide (12.78 mg, 29.52 umol, 21.52% yield, 96.878% purity) was obtained as a white solid. MS (ESI) *m/z* 423.2 $[M+H]^+$

[0001172] Prep-HPLC condition: column: Waters Xbridge BEH C18 100*25mm*5 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 25%-55%,10 min.

[0001173] Column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-55%,8 min.

[0001174] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.61 (dd, *J* = 7.03, 1.77 Hz, 1 H), 9.49 (dd, *J* = 17.24, 7.83 Hz, 1 H), 8.59 - 8.71 (m, 2 H), 8.53 (d, *J* = 7.82 Hz, 1 H), 7.85 - 7.93 (m, 1 H), 7.47 - 7.55 (m, 1 H), 7.38 (t, *J* = 2.51 Hz, 1 H), 7.06 - 7.14 (m, 1 H), 7.01 - 7.01 (m, 1 H), 7.01 (dd, *J* = 8.25, 3.24 Hz, 1 H), 6.51 (dd, *J* = 7.70, 1.34 Hz, 1 H), 6.32 (dd, *J* = 12.41, 7.76 Hz, 1 H), 4.44 - 4.61 (m, 1 H), 3.89 (d, *J* = 1.10 Hz, 3 H), 1.62 - 1.81 (m, 2 H), 1.46 - 1.60 (m, 1 H), 0.81 - 1.03 (m, 7 H).

Step 6: (S)-tert-butyl 2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoate

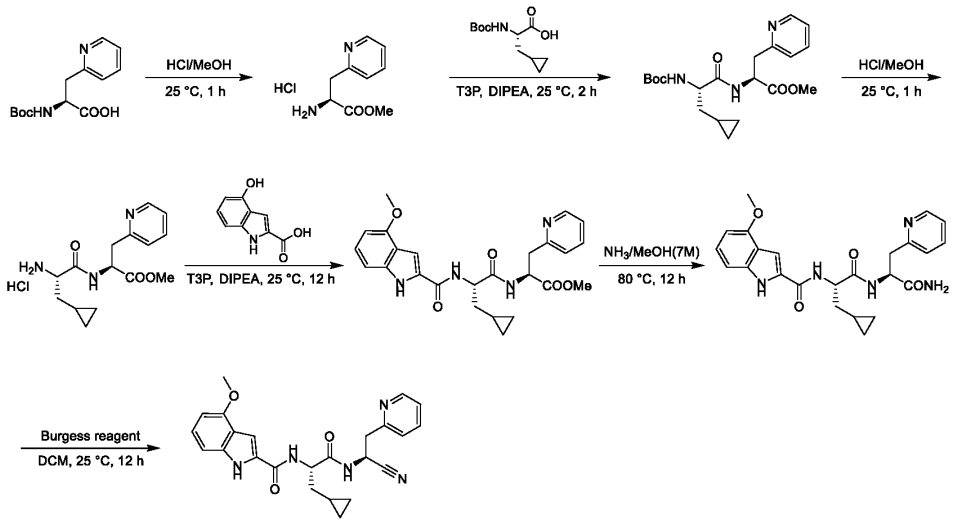
[0001175] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (15 g, 78.46 mmol, 1 *eq*) and tert-butyl (2S)-2-amino-4-methyl-pentanoate (21.07 g, 94.15 mmol, 1.2 *eq*, HCl) in DMF (150 mL) was added EDCI (19.55 g, 102.00 mmol, 1.3 *eq*), HOBt (13.78 g, 102.00 mmol, 1.3 *eq*), TEA (23.82 g, 235.38 mmol, 32.76 mL, 3 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was added water (450 mL) and extracted with ethyl acetate (250 mL * 3) to get the organic phase. The organic phase was washed with 5% citric acid (300 mL) and 5% aqueous solution of sodium bicarbonate (300 mL) and dried over anhydrous sodium sulfate, filtered and concentrated to get the product. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate=30:1 to 10:1) to afford tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl- pentanoate (24 g, 66.58 mmol, 84.87% yield) as light yellow solid. MS (ESI) *m/z* 361.2 $[M+H]^+$

Step 7: (S)-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanoic acid

[0001176] To a mixture of tert-butyl (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoate (10 g, 27.74 mmol, 1 *eq*) in DCM (30 mL) was added TFA (61.60 g, 540.26 mmol, 40 mL, 19.47 *eq*) and H_2O (4.00 g, 221.98 mmol, 4.00 mL, 8.00 *eq*) in one

portion at 0 °C under N_2. The mixture was stirred at 25 °C and stirred for 2 h. The reaction mixture was concentrated to get the crude product. The crude product was purified by pulping with petroleum ether:ethyl acetate = 10:1 (20 mL) and filtered to get the product. (2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoic acid (6 g, 19.22 mmol, 69.27% yield, 97.48% purity) was obtained as a light yellow solid. MS (ESI) *m/z* 305.1 $[M+H]^+$

Example 134. Synthesis of viral protease inhibitor compound 439



Step 1: methyl (2S)-2-amino-3-(2-pyridyl)propanoate

[0001177] To a mixture of (2S)-2-(tert-butoxycarbonylamino)-3-(2-pyridyl)propanoic acid (1 g, 3.76 mmol, 1 *eq*) was added HCl/MeOH (4 M, 10 mL, 10.65 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 1h. The reaction mixture was concentrated to get the product. Methyl (2S)-2-amino-3-(2-pyridyl)propanoate (900 mg, 3.48 mmol, 92.79% yield, 98% purity, 2HCl) was obtained as a white solid and used directly next step. MS (ESI) *m/z* 181.1 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(2- pyridyl)propanoate

[0001178] To a mixture of methyl (2S)-2-amino-3-(2-pyridyl)propanoate (0.9 g, 3.56 mmol, 1 *eq*, 2HCl) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (978.23 mg, 4.27 mmol, 1.2 *eq*) and DIPEA (2.30 g, 17.78 mmol, 3.10 mL, 5 *eq*) in DCM (6 mL) and THF (6 mL) was added T_3P (3.39 g, 5.33 mmol, 3.17 mL, 50% purity, 1.5 *eq*)

at 0 °C under N_2. The mixture was stirred at 25 °C for 2 h. The reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL x 2) to get the organic phase. The organic phase was concentrated to get the crude product. Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino] -3-(2-pyridyl)propanoate (1.1 g, 2.81 mmol, 79.03% yield) was obtained as a light yellow solid and used directly next step. MS (ESI) m/z 392.2 $[M+H]^+$

Step 3: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(2-pyridyl)propanoate

[0001179] To a mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3- (2-pyridyl)propanoate (1.1 g, 2.81 mmol, 1 *eq*) was added HCl/MeOH (4 M, 11 mL, 15.66 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated to get the product. Methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(2-pyridyl)propanoate (1 g, crude, HCl) was obtained as a brown solid and used directly next step. MS (ESI) *m/z* 292.2 $[M+H]^+$

Step 4: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl] amino]-3-(2-pyridyl)propanoate

[0001180] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3- (2-pyridyl)propanoate (0.8 g, 2.20 mmol, 1 *eq*, 2HCl) and 4-methoxy-1H-indole-2-carboxylic acid (461.86 mg, 2.42 mmol, 1.1 *eq*) and DIPEA (1.42 g, 10.98 mmol, 1.91 mL, 5 *eq*) in DCM (0.5 mL) and THF (0.5 mL) was added T_3P (2.10 g, 3.29 mmol, 1.96 mL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was added saturated sodium bicarbonate solution (10 mL) and extracted with DCM (10 mL x 2) to get the organic phase. The organic phase was concentrated to get the crude product. The residue was purified by flash silica gel chromatography. Methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino] propanoyl]amino]-3-(2-pyridyl)propanoate (0.8 g, 1.50 mmol, 68.38% yield, 87.2% purity) was obtained as a light yellow solid. MS (ESI) *m/z* 465.2 $[M+H]^+$

Step 5: N-[(1S)-1-(cyclopropylmethyl)-2-[[(1S)-1-(nitrosomethyl)-2-(2-pyridyl)ethyl]amino]-2-oxo -ethyl]-4-methoxy-1H-indole-2-carboxamide

[0001181] To a mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino] propanoyl]amino]-3-(2-pyridyl)propanoate (0.2 g, 430.56 umol, 1 *eq*) was added NH_3/MeOH (7 M, 4 mL, 65.03 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to 25 °C and concentrated to get the crude product. N-[(1S)-1-(cyclopro pylmethyl)-2-[[(1S)-1-(nitrosomethyl)-2-(2-pyridyl)ethyl]amino]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (200 mg, crude) was obtained as a light yellow solid and used directly next step. MS (ESI) *m/z* 450.2 $[M+H]^+$

Step 6: N-[(1S)-2-[[(1S)-1-cyano-2-(2-pyridyl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4- methoxy-1H-indole-2-carboxamide

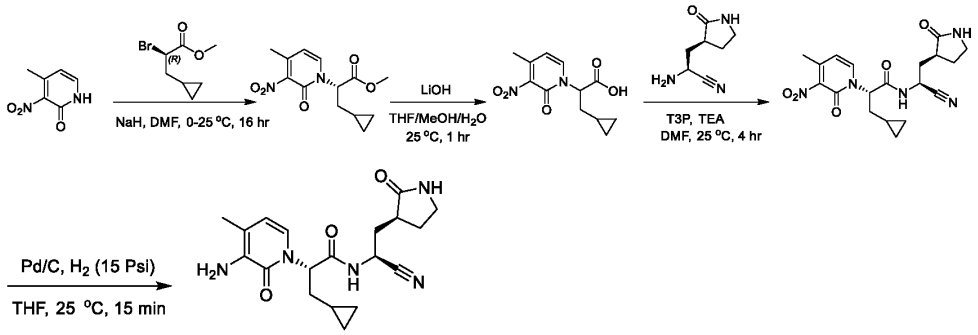
[0001182] To a mixture of N-[(1S)-1-(cyclopropylmethyl)-2-[[(1S)-1-(nitrosomethyl)-2-(2-pyridyl)ethyl]ami no]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (0.1 g, 222.47 umol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (212.06 mg, 889.88 umol, 4 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to get the crude product. The crude product was purified by pre-HPLC. N-[(1S)-2-[[(1S)-1-cyano-2-(2-pyridyl)ethyl]amino] -1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (25.44 mg, 58.27 umol, 26.19% yield, 98.833% purity) was obtained as a white solid. MS (ESI) *m/z* 432.2 $[M+H]^+$

[0001183] Prep-HPLC condition: column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 30%-50%,8 min

[0001184] ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.27 - 8.39 (m, 1 H), 7.64 - 7.73 (m, 1 H), 7.31 - 7.39 (m, 1 H), 7.23 - 7.30 (m, 1 H), 7.12 - 7.23 (m, 2 H), 7.00 - 7.07 (m, 1 H), 6.52 (d, J = 7.50 Hz, 1 H), 5.28 (t, J = 7.17 Hz, 1 H), 4.51 - 4.63 (m, 1 H), 3.87 - 3.98 (m, 3 H), 3.30 - 3.31 (m, 2 H), 1.57 - 1.83 (m, 2 H), 0.62 - 0.85 (m, 1 H), 0.34 - 0.54 (m, 2 H), 0.05 - 0.22 (m, 2 H).

[0001185] ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.35 (br s, 1 H), 8.50 - 8.68 (m, 1 H), 8.04 - 8.26 (m, 1 H), 7.51 (td, J=7.69, 1.75 Hz, 1 H), 6.93 - 7.11 (m, 4 H), 6.77 - 6.90 (m, 2 H), 6.34 - 6.42 (m, 1 H), 5.11 - 5.23 (m, 1 H), 4.61 - 4.71 (m, 1 H), 3.76 - 3.87 (m, 3 H), 3.07 - 3.25 (m, 2 H), 1.55 - 1.69 (m, 2 H), 0.48 - 0.67 (m, 1 H), 0.28 - 0.40 (m, 2 H), -0.09 - 0.08 (m, 2 H).

Example 135. Synthesis of viral protease inhibitor compound 448



Step 1: Methyl (2S)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate

[0001186] A solution of 4-methyl-3-nitro-1*H*-pyridin-2-one (500 mg, 3.24 mmol, 1 *eq*) in DMF (10 mL) was added NaH (181.6 mg, 4.54 mmol, 60% purity, 1.4 *eq*) at 0 °C, and the reaction mixtue was stirred at 25 °C for 0.5 hr. Then methyl (2*R*)-2-bromo-3-cyclopropyl-propanoate (671.7 mg, 3.24 mmol, 1 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 16 h under N_2. LCMS showed one peak with desired MS was detected. The mixture was quenched with H_2O (50 mL), and extracted with ethyl acetate (150 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/petroleum ethergradient @ 35 mL/min) to give methyl (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate (453 mg, 45.1% yield) as a yellow solid.

[0001187] LCMS: Rt = 0.780 min; for $C_{13}H_{16}N_2O_5$ MS Calcd.: 280.11; MS Found: 281.0 [$M+H^+$].

[0001188] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, *J* = 7.03 Hz, 1H), 6.43 (d, *J* = 7.03 Hz, 1H), 5.30 (t, *J* = 7.65 Hz, 1H), 3.65 (s, 3H), 2.23 (s, 3H), 1.99 (t, *J* = 7.40 Hz, 2H), 0.56 - 0.45 (m, 1H), 0.38 - 0.25 (m, 2H), 0.15 - 0.13 (m, 2H).

Step 2: (2S)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid

[0001189] A mixture of methyl (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate (253 mg, 0.90 mmol, 1 *eq*), LiOH.H_2O (151.5 mg, 3.61 mmol, 4

eq) in THF (2.1 mL), MeOH (0.7 mL), H_2O (0.7 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. LCMS showed one peak with desired MS was detected. The mixture was added H_2O (5 mL), then the mixture was added 2 M HCl (2 mL) to adjust the pH to about 6~7. The mixture was added H_2O (10 mL), and extracted with ethyl acetate (30 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure to give (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid (207 mg, 77.9% yield) as a yellow solid.

[0001190] LCMS: Rt = 0.732 min; for $C_{12}H_{14}N_2O_5$ MS Calcd.: 266.09; MS Found: 267.0 [$M+H^+$].

Step 3: (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide

[0001191] To a solution of (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid (207 mg, 0.77 mmol, 1 *eq*) in DMF (2 mL) was added T_3P (989.5 mg, 1.55 mmol, 0.92 mL, 50% purity, 2 *eq*), TEA (314.6 mg, 3.11 mmol, 0.43 mL, 4 *eq*)and (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanenitrile (147.4 mg, 0.77 mmol, 1 *eq*, HCl). The mixture was stirred at 25 °C for 4 h. LCMS showed the peak with desired MS was detected. The mixture was quenched with H_2O (20 mL), and extracted with ethyl acetate (30 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @ 30 mL/min) to give Compound (2S)-*N*-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide (60 mg, 17.8% yield) as a yellow solid.

[0001192] LCMS: Rt = 1.336 min; for $C_{19}H_{23}N_5O_5$ MS Calcd.: 401.17; MS Found: 402.1 [$M+H^+$].

(2S)-2-(3-amino-4-methyl-2-oxo-1-pyridyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide

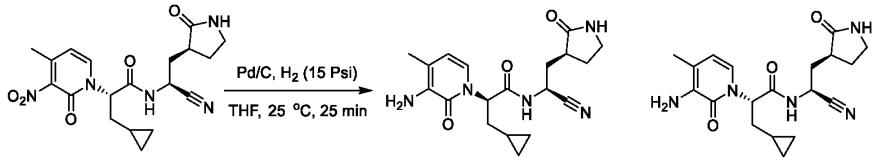
[0001193] To a solution of (2*S*)-*N*-[(1S)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide (60 mg, 0.14 mmol, 1

eq) in THF (2 mL) was added Pd/C (70 mg, 65.7 umol, 10% purity, 0.44 *eq*). The mixture was stirred at 25 °C for 15 min under H_2. LCMS showed one peak with desired MS was detected. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80 *30 mm *3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 13%-43%,9.5 min) to give (2*S*)-2-(3-amino-4-methyl-2-oxo-1-pyridyl)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (7.45 mg, 19.7 umol, 13.2% yield, 98.4% purity) as a brown solid.

[0001194] LCMS： Rt = 0.698 min; for $C_{19}H_{25}N_5O_3$ MS Calcd.: 371.20; MS Found: 372.1 [$M+H^+$].

[0001195] ^1H NMR (400 MHz, CD_3OD) δ 6.94 - 6.82 (m, 1H), 6.11 - 6.01 (m, 1H), 5.40 - 5.23 (m, 1H), 4.86 (br dd, *J*=6.0, 9.8 Hz, 1H), 3.14 - 3.08 (m, 2H), 2.47 - 2.27 (m, 1H), 2.23 - 2.03 (m, 2H), 1.99 - 1.91 (m, 3H), 1.83 - 1.57 (m, 4H), 0.48 (br d, *J*=7.3 Hz, 1H), 0.34 - 0.19 (m, 2H), 0.02 - 0.16 (m, 2H).

Example 136. Synthesis of viral protease inhibitor compound 449



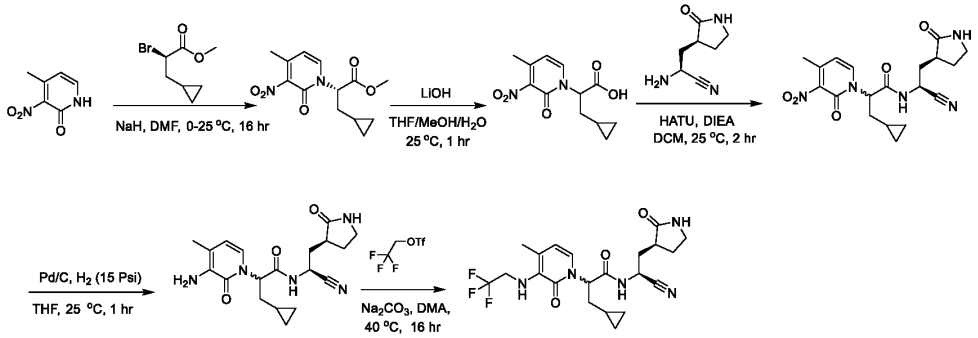
[0001196] To a solution of (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide (345.0 mg, 0.85 mmol, 1 eq) in THF (5 mL) was added Pd/C (233.1 mg, 0.21 mmol, 10% purity). The mixture was stirred at 25 °C for 25 min under H_2. LCMS showed one peak with desired MS was detected. The reaction mixture was filtered and the filtrate was quenched with H_2O (20 mL), and extracted with ethyl acetate (30 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @ 30 mL/min) to give the product (203 mg).70 mg of product was separated by SFC (column: DAICEL CHIRALPAK AD(250 mm * 30 mm, 10 um);mobile phase: [0.1% NH_3H_2O IPA];B%:

45%-45%, min) to give 2-[(1S)-3-amino-4-methyl-2-oxo-1-pyridyl]-*N*-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (20.08 mg, 6.2% yield) and 2-[(1*R*)-3-amino-4-methyl-2-oxo-1-pyridyl]-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (23.04 mg, 7.0% yield) as a white solid.

[0001197] Isomer 1: LCMS： Rt = 0.659 min; for $C_{19}H_{25}N_5O_3$ MS Calcd.: 371.20; MS Found: 394.1 [M+Na$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J*=7.0 Hz, 1H), 6.22 (d, *J*=7.1 Hz, 1H), 5.50 (t, *J*=7.8 Hz, 1H), 5.04 - 4.98 (m, 1H), 3.37 - 3.32 (m, 2H), 2.52 - 2.46 (m, 1H), 2.38 - 2.24 (m, 2H), 2.11 (s, 3H), 1.94 - 1.81 (m, 4H), 0.61 - 0.56 (m, 1H), 0.42 - 0.38 (m, 2H), 0.13 - 0.02 (m, 2H).

[0001198] Isomer 2: LCMS： Rt = 0.704 min; for $C_{19}H_{25}N_5O_3$ MS Calcd.: 371.20; MS Found: 372.1 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (d, *J*=7.1 Hz, 1H), 6.20 (d, *J*=7.0 Hz, 1H), 5.41 (dd, *J*=7.1, 8.4 Hz, 1H), 5.00 (br dd, *J*=6.1, 10.0 Hz, 1H), 3.29 - 3.24 (m, 2H), 2.49 (dq, *J*=5.4, 9.3 Hz, 1H), 2.31 - 2.21 (m, 2H), 2.09 (s, 3H), 1.98 - 1.76 (m, 4H), 0.69 - 0.57 (m, 1H), 0.50 - 0.41 (m, 2H), 0.17 - 0.04 (m, 2H).

Example 137. Synthesis of viral protease inhibitor compound 450



Step 1: Methyl (2S)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate

[0001199] To a solution of 4-methyl-3-nitro-1*H*-pyridin-2-one (1 g, 6.49 mmol, 1 *eq*) in DMF (15 mL) was added NaH (363.3 mg, 9.08 mmol, 60% purity, 1.4 *eq*) at 0 °C, and the reaction mixture was stirred at 25 °C for 0.5 hr. Then methyl (2*R*)-2-bromo-3-cyclopropyl-propanoate (1.34 g, 6.49 mmol, 1 *eq*) was added at 0 °C. The mixture was stirred at 25 °C for 16 h under N_2. LCMS showed one peak with desired MS was

detected. The mixture was quenched with H_2O (20 mL), and extracted with ethyl acetate (50 mL * 3). The combined organic layers was washed with brine (40 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 35 mL/min) to give methyl (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate (867 mg, 47.4% yield) as a yellow solid.

[0001200] LCMS: Rt = 0.785 min; for $C_{13}H_{16}N_2O_5$ MS Calcd.: 280.11; MS Found: 281.1 [$M+H^+$].

Step 2: (2S)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid

[0001201] A mixture of methyl (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate (867 mg, 3.09 mmol, 1 *eq*), $LiOH.H_2O$ (519.2 mg, 12.37 mmol, 4 *eq*) in THF (6 mL), MeOH (2 mL), H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 h under N_2 atmosphere. LCMS showed one peak with desired MS was detected. The mixture was added H_2O (5 mL), then the mixture was added 2 M HCl (4 mL) to adjust the pH to about 6~7. The mixture was extracted with ethyl acetate (30 mL * 3). The combined organic layers was washed with brine (20 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure to give product. Compound (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid (791 mg, 94.8% yield) was obtained as a yellow solid.

[0001202] LCMS: Rt = 0.735 min; for $C_{12}H_{14}N_2O_5$ MS Calcd.: 266.09; MS Found: 267.0 [$M+H^+$].

Step 3: N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide

[0001203] To a solution of (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid (791 mg, 2.97 mmol, 1 *eq*) in DCM (10 mL) was added HATU (1.36 g, 3.57 mmol, 1.2 *eq*), DIPEA (1.15 g, 8.91 mmol, 1.55 mL, 3 *eq*) and (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanenitrile (676.0 mg, 3.57 mmol, 1.2 *eq*, HCl). The mixture was stirred at 25 °C for 2 h. LCMS showed one peak with desired MS was detected. The mixture was quenched with H_2O (20 mL), and extracted with DCM (40

mL * 3). The combined organic layers was washed with brine (20 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH ethergradient @ 35 mL/min) to give *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide (838 mg, 64.5% yield) as yellow oil. LCMS： Rt = 0.741 min; for $C_{19}H_{23}N_5O_5$ MS Calcd.: 401.17; MS Found: 402.1 [$M+H^+$].

Step 4: 2-(3-Amino-4-methyl-2-oxo-1-pyridyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide

[0001204] To a solution of *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide (838 mg, 2.09 mmol, 1 *eq*) in THF (10 mL) was added Pd/C (566.5 mg, 0.53 mmol, 10% purity). The mixture was stirred at 25 °C for 1 h under H_2. LCMS showed one peak with desired MS was detected. The mixture was filtered and concentrated under reduce pressure to give 2-(3-amino-4-methyl-2-oxo-1-pyridyl)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (616 mg, 68.7% yield) as a white solid.

[0001205] LCMS： Rt = 0.703 min; for $C_{19}H_{25}N_5O_3$ MS Calcd.: 371.20; MS Found: 372.1 [$M+H^+$].

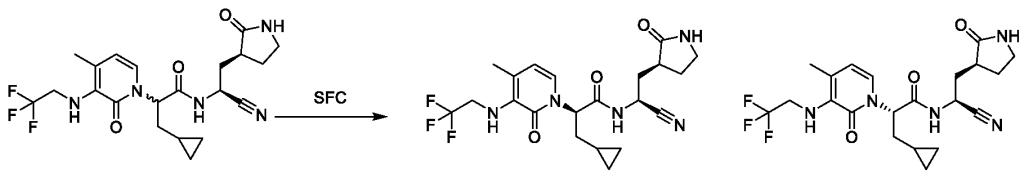
N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[4-methyl-2-oxo-3-(2,2,2-trifluoroethylamino)-1-pyridyl]propanamide

[0001206] To a solution of 2-(3-amino-4-methyl-2-oxo-1-pyridyl)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (100 mg, 0.26 mmol, 1 *eq*) in DMA (5 mL) was added Na_2CO_3 (730.5 mg, 6.89 mmol, 25.60 *eq*) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.6 g, 6.89 mmol, 25.6 *eq*). The mixture was stirred at 40 °C for 16 h. The mixture was filtered, and then the filtrate was quenched with H_2O (20 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80 * 40 mm * 3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 23%-53%,7.8 min). Compound *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-

yl]ethyl]-3-cyclopropyl-2-[4-methyl-2-oxo-3-(2,2,2-trifluoroethylamino)-1-pyridyl]propanamide (71.7 mg, 57.9% yield) was obtained as a white solid. LCMS: Rt = 0.794 min; for $C_{21}H_{26}F_3N_5O_3$ MS Calcd.: 453.20; MS Found: 454.1 [M+H$^+$].

[0001207] ^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (dd, *J*=3.9, 7.2 Hz, 1H), 6.22 (dd, *J*=5.5, 7.0 Hz, 1H), 5.52 - 5.32 (m, 1H), 5.01 (dd, *J*=6.1, 9.9 Hz, 1H), 4.03 - 3.73 (m, 2H), 3.36 - 3.32 (m, 1H), 3.29 - 3.21 (m, 1H), 2.56 - 2.45 (m, 1H), 2.41 - 2.22 (m, 2H), 2.21 (d, *J*=5.3 Hz, 3H), 2.04 - 1.91 (m, 2H), 1.91 - 1.71 (m, 2H), 0.67 - 0.55 (m, 1H), 0.48 - 0.35 (m, 2H), 0.18 -0.02 (m, 2H).

Example 138. Synthesis of viral protease inhibitor compound 451



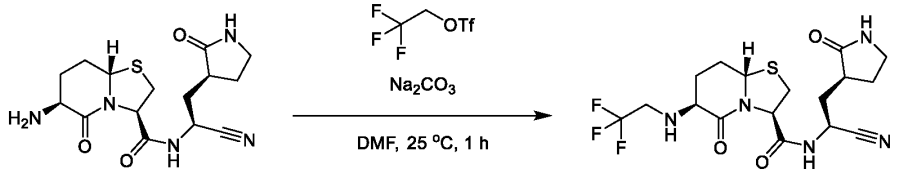
[0001208] *N*-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[4-methyl-2-oxo-3-(2,2,2-trifluoroethylamino)-1-pyridyl]propanamide (69 mg, 0.15 mmol, 1 eq) was separated by SFC(condition:column: DAICEL CHIRALPAK AD(250 mm * 30 mm, 10 um);mobile phase: [0.1% NH3H2O ETOH];B%: 45%-45%, min) to afford (2R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[4-methyl-2-oxo-3-(2,2,2-trifluoroethylamino)-1-pyridyl]propanamide (17.12 mg, 24.8% yield) as a white solid.

[0001209] Isomer 1: LCMS: Rt = 0.799 min; for $C_{21}H_{26}F_3N_5O_3$ MS Calcd.: 453.20; MS Found: 454.1 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (d, *J*=7.0 Hz, 1H), 6.23 (d, *J*=7.3 Hz, 1H), 5.45 (t, *J*=7.8 Hz, 1H), 5.01 (dd, *J*=6.7, 9.4 Hz, 1H), 4.03 - 3.70 (m, 2H), 3.36 - 3.32 (m, 2H), 2.56 - 2.46 (m, 1H), 2.41 - 2.24 (m, 2H), 2.21 (s, 3H), 1.98 - 1.93 (m, 2H), 1.93 - 1.76 (m, 2H), 0.64 - 0.50 (m, 1H), 0.44 - 0.33 (m, 2H), 0.17 - 0.04 (m, 2H).

[0001210] Isomer 2: LCMS: Rt = 0.800 min; for $C_{21}H_{26}F_3N_5O_3$ MS Calcd.: 453.20; MS Found: 454.1 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (d, *J*=7.3 Hz, 1H), 6.22 (d, *J*=7.0 Hz, 1H), 5.38 (dd, *J*=7.0, 8.5 Hz, 1H), 5.01 (dd, *J*=6.0, 10.0 Hz, 1H), 3.89 (q, *J*=9.5 Hz, 2H), 3.30 - 3.21 (m, 2H), 2.50 (dq, *J*=5.3, 9.3 Hz, 1H), 2.32 - 2.22 (m, 2H), 2.20 (s,

3H), 2.06 - 1.90 (m, 2H), 1.89 - 1.68 (m, 2H), 0.69 - 0.57 (m, 1H), 0.50 - 0.36 (m, 2H), 0.22 - 0.04 (m, 2H).

Example 139. Synthesis of viral protease inhibitor compound 455

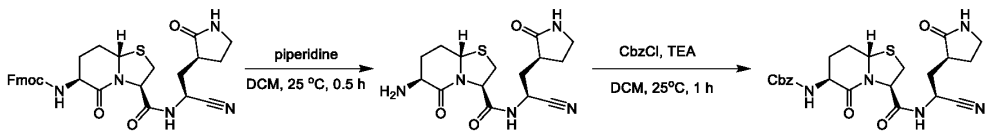


[0001211] To a solution of (3R,6S)-6-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridine-3-carboxamide (40.0 mg, 0.11 mmol, 1 *eq*) in DMF (0.5 mL) was added Na_2CO_3 (24.1 mg, 0.22 mmol, 2 *eq*) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (26.4 mg, 0.11 mmol, 1 *eq*). The mixture was stirred at 25 °C for 1 h. The reaction mixture was added H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH4HCO3)-ACN];B%: 8%-38%, 9.5 min). (3R,6S,8aS)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5-oxo-6-(2,2,2-trifluoroethylamino)-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridine-3-carboxamide (8.02 mg, 18.5 umol, 16.2% yield, 100% purity) was obtained as a white solid.

[0001212] LCMS: Rt = 0.686 min; for $C_{17}H_{22}F_3N_5O_3S$ MS Calcd.: 433.45; MS Found: 434.0 [$M+H^+$].

[0001213] ^1H NMR (400 MHz, CD_3OD) δ 5.02 (dd, *J* = 10.79, 5.27 Hz, 1 H), 4.90 - 4.98 (m, 2 H), 4.77 - 4.83 (m, 1 H), 3.33 - 3.49 (m, 4 H), 3.20 - 3.29 (m, 1 H), 3.11 - 3.20 (m, 1 H), 2.67 (qd, *J* = 9.29, 5.27 Hz, 1 H), 2.17 - 2.45 (m, 4 H), 1.72 - 1.99 (m, 4 H).

Example 140. Synthesis of viral protease inhibitor compound 457



(3R,6S,8aS)-6-amino-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-5-oxohexahydro-2H-thiazolo[3,2-a]pyridine-3-carboxamide

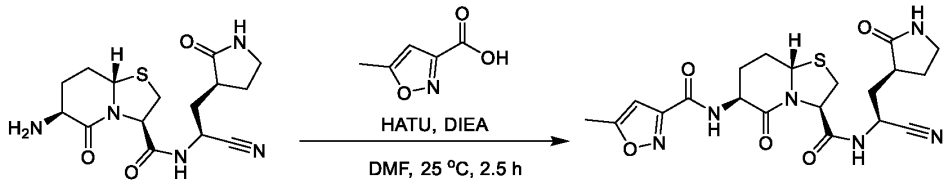
[0001214] To a solution of 9H-fluoren-9-ylmethyl N-[(3R,6S)-3-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridin-6-yl]carbamate (50 mg, 87.1 umol, 1 *eq*) in DCM (0.2 mL) was added piperidine (14.8 mg, 0.17 mmol, 17 uL, 2 *eq*). The mixture was stirred at 25 °C for 0.5 hr. Compound (3R,6S)-6-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridine-3-carboxamide (30 mg, crude) was obtained as a yellow oil.

Benzyl((3R,6S,8aS)-3-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)carbamoyl)-5-oxohexahydro-2H-thiazolo[3,2-a]pyridin-6-yl)carbamate

[0001215] To a solution of (3R,6S)-6-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridine-3-carboxamide (30 mg, 85.3 umol, 1 *eq*) in DCM (1 mL) was added benzyl carbonochloridate (29.1 mg, 0.17 mmol, 24 uL, 2 *eq*) and TEA (25.9 mg, 0.25 mmol, 35 uL, 3 *eq*). The mixture was stirred at 25 °C for 2 h. LCMS detected desired compound. The reaction mixture was added H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH4HCO3)-ACN]; B%: 15%-45%, 9.5 min). Then the residue was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5 um; mobile phase: [water (0.04% NH_3H_2O+10 mM NH4HCO3)-MeOH]; B%: 40%-80%, 9.5 min). Compound benzyl N-[(3R,6S)-3-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridin-6-yl]carbamate (1.41 mg, 2.8 umol, 3.3% yield, 99% purity) was obtained as a white solid. LCMS: Rt = 0.751 min; for $C_{23}H_{27}N_5O_5S$ MS Calcd.: 485.56; MS Found: 486.1 [$M+H^+$].

[0001216] ^1H NMR (400 MHz, $CDCl_3$) δ8.32 (br s, 1 H), 7.37 (br s, 5 H), 6.07 (br s, 1 H), 5.67 (br s, 1 H), 5.38 (br s, 1 H), 5.17 (br d, *J* = 10.26 Hz, 2 H), 4.90 (br s, 1 H), 4.80 (br s, 1 H), 3.97 (br s, 1 H), 3.52 (br s, 1 H), 3.25 (br s, 1 H), 3.33 (br s, 3 H), 2.44 (br s, 1 H), 2.33 (br d, *J* = 15.38 Hz, 1 H), 1.97 - 2.13 (m, 2 H), 1.85 (br s, 3 H).

Example 141. Synthesis of viral protease inhibitor compound 459

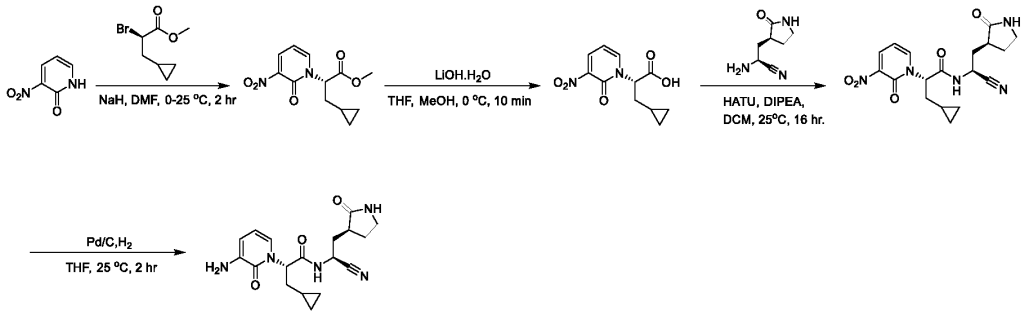


N-((3R,6S,8aS)-3-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)carbamoyl)-5-oxohexahydro-2H-thiazolo[3,2-a]pyridin-6-yl)-5-methylisoxazole-3-carboxamide

[0001217] A mixture of 5-methylisoxazole-3-carboxylic acid (36.1 mg, 0.28 mmol, 2 *eq*), HATU (108.2 mg, 0.28 mmol, 2 *eq*) and DIEA (73.5 mg, 0.56 mmol, 99 uL, 4 *eq*) in DMF (1 mL) was stirred at 25 °C for 0.5 h, and then (3R,6S)-6-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridine-3-carboxamide (50.0 mg, 0.14 mmol, 1 *eq*) was added into the reaction. The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was added H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 7%-37%,9.5 min). Compound N-[(3R,6S,8aS)-3-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridin-6-yl]-5-methyl-isoxazole-3-carboxamide (15.28 mg, 33.0 umol, 23.2% yield, 99.7% purity) was obtained as a white solid. LCMS: Rt = 0.698 min; for $C_{20}H_{24}N_6O_5S$ MS Calcd.: 460.51; MS Found: 461.1 [$M+H^+$].

[0001218] ^1H NMR (400 MHz, CD_3OD) δ ppm 6.52 (d, *J* = 0.75 Hz, 1 H), 4.98 - 5.07 (m, 3 H), 4.44 (dd, *J* = 11.17, 6.90 Hz, 1 H), 3.41 (dd, *J* = 11.67, 7.65 Hz, 1 H), 3.23 - 3.29 (m, 3 H), 2.58 - 2.69 (m, 1 H), 2.48 (s, 3 H), 2.27 - 2.44 (m, 4 H), 2.08 - 2.21 (m, 1 H), 1.79 - 2.01 (m, 3 H).

Example 142. Synthesis of viral protease inhibitor compound 465



Methyl (2S)-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanoate

[0001219] To a solution of 3-nitro-1*H*-pyridin-2-one (1 g, 7.14 mmol, 1 *eq*) in DMF (10 mL) was added NaH (428.2 mg, 10.71 mmol, 60% purity, 1.5 eq) at 0 °C for 15 min. Then, methyl (2R)-2-bromo-3-cyclopropyl-propanoate (1.6 g, 7.85 mmol, 1.1 eq) was added into the mixture, and the mixture was stirred at 25 °C for 2 hr. TLC (petroleum ether: ethyl acetate = 1:1) showed new spot was detected. The reaction mixture was quenched by addition H2O (10 mL) at 0 °C, and extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~50% petroleum ether/ethyl acetate ethergradient @ 30 mL/min) to give methyl (2*S*)-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanoate (552 mg, 28.7% yield, 98.9% purity) as a yellow solid.

(2S)-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanoic acid

[0001220] To a solution of methyl (2*S*)-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanoate (230 mg, 0.86 mmol, 1 *eq*) in THF (1 mL) and MeOH (0.2 mL) was added $LiOH.H_2O$ (108.7 mg, 2.59 mmol, 3 *eq*) in H_2O (0.2 mL). The mixture was stirred at 0 °C for 10 min. LC-MS showed the desired compound was detected. The reaction was adjusted with 4 M HCl to pH = 4. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic phase was washed with brine (5 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was used into the next step without further purification. Compound (2*S*)-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanoic acid (210 mg, 96.3% yield) was obtained as a yellow solid.

(2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanamide

[0001221] To a solution of (2*S*)-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanoic acid (260 mg, 1.03 mmol, 1 *eq*) in DCM (3 mL) was added HATU (470.3 mg, 1.24 mmol, 1.2 *eq*), DIPEA (266.4 mg, 2.06 mmol, 0.35 mL, 2 *eq*) and (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanenitrile (234.5 mg, 1.24 mmol, 1.2 *eq*, HCl). The mixture was stirred at 25 °C for 16 h. TLC (DCM /MeOH = 10:1) showed new spot was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH ethergradient @ 20 mL/min) to give (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanamide (225 mg, 54.0% yield, 96% purity) as a yellow solid.

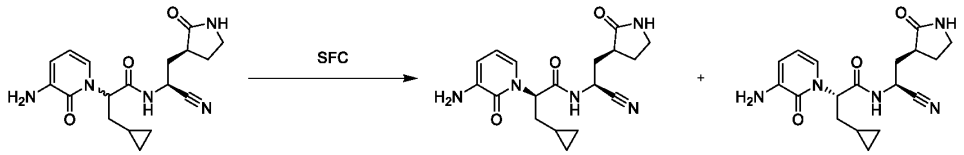
(2S)-2-(3-amino-2-oxo-1-pyridyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide

[0001222] To a solution of (2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(3-nitro-2-oxo-1-pyridyl)propanamide (200 mg, 0.51 mmol, 1 *eq*) in THF (0.5 mL) was added Pd/C (200 mg, 0.18 mmol, 10% purity, 3.64e-1 *eq*) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 10 min. LC-MS showed the desired compound was detected. TLC (DCM/MeOH = 10:1) showed new spot was detected. The resulting product was dissolved in MeOH (5 mL) and filtered to remove the insoluble. The filter liquor was concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~5% petroleum ether/ethyl acetate ethergradient @ 20 mL/min) to give (2*S*)-2-(3-amino-2-oxo-1-pyridyl)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (119 mg, 64.3% yield, 99.7% purity) as a brown solid.

[0001223] LCMS: Rt = 0.669 min; for $C_{18}H_{23}N_5O_3$ MS Calcd.: 357.18; MS Found: 358.1 [$M+H^+$].

[0001224] ^{1}H NMR (400 MHz, CD_3OD) δ 7.06 - 7.01 (m, 1H), 6.70 - 6.64 (m, 1H), 6.24 (s, 1H), 5.56 - 5.41 (m, 1H), 5.06 - 4.97 (m, 1H), 3.30 - 3.24 (m, 2H), 2.57 - 2.43 (m, 1H), 2.38 - 2.18 (m, 2H), 2.04 - 1.85 (m, 3H), 1.85 - 1.69 (m, 1H), 0.70 - 0.54 (m, 1H), 0.50 - 0.36 (m, 2H), 0.21 - 0.12 (m, 1H), 0.10 - 0.02 (m, 1H).

Example 143. Synthesis of viral protease inhibitor compound 465

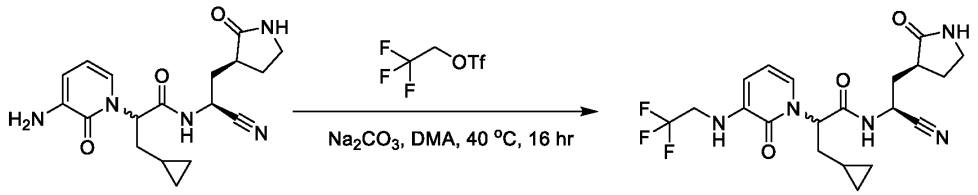


[0001225] The residue was purification by SFC. LC-MS showed the desired compound was detected. The residue was purified by SFC (column: DAICEL CHIRALPAK AS (250 mm*30 mm, 10 um); mobile phase: [0.1% NH_3H_2O EtOH]; B%: 30%-30%, min).

[0001226] Isomer 1: 2-[(1*S*)-3-amino-2-oxo-1-pyridyl]-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (2.84 mg, 6.3% yield, 98.9% purity) as a brown solid. LCMS: Rt = 0.660 min; for $C_{18}H_{23}N_5O_3$ MS Calcd.: 357.41; MS Found: 358.1 [$M+H^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (dd, *J* = 1.4, 7.0 Hz, 1H), 6.68 (dd, *J* = 1.4, 7.2 Hz, 1H), 6.26 (t, *J* = 7.1 Hz, 1H), 5.53 (t, *J* = 7.7 Hz, 1H), 5.02 (dd, *J* = 6.8, 9.3 Hz, 1H), 3.38 - 3.32 (m, 2H), 2.56 - 2.46 (m, 1H), 2.36 (m, 1H), 2.32 - 2.23 (m, 1H), 1.97 - 1.87 (m, 3H), 1.87 - 1.79 (m, 1H), 0.67 - 0.54 (m, 1H), 0.45 - 0.34 (m, 2H), 0.19 - 0.10 (m, 1H), 0.07 - 0.02 (m, 1H).

[0001227] Isomer 2: Compound 2-[(1*R*)-3-amino-2-oxo-1-pyridyl]-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (21.3 mg, 46.5% yield) was obtained as a brown solid. LCMS: Rt = 0.671 min; for $C_{18}H_{23}N_5O_3$ MS Calcd.: 357.41; MS Found: 358.1 [$M+H^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.04 (dd, *J* = 1.5, 7.0 Hz, 1H), 6.67 (dd, *J* = 1.5, 7.3 Hz, 1H), 6.24 (t, *J* = 7.1 Hz, 1H), 5.44 (t, *J* = 7.7 Hz, 1H), 5.01 (dd, *J* = 6.1, 10.1 Hz, 1H), 3.30 - 3.24 (m, 2H), 2.49 (dq, *J* = 5.4, 9.3 Hz, 1H), 2.32 - 2.20 (m, 2H), 2.01 - 1.83 (m, 3H), 1.83 - 1.70 (m, 1H), 0.70 - 0.59 (m, 1H), 0.51 - 0.38 (m, 2H), 0.20 - 0.12 (m, 1H), 0.10 - 0.00 (m, 1H).

Example 144. Synthesis of viral protease inhibitor compound 466



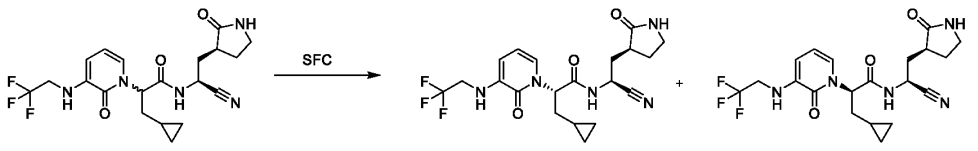
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[2-oxo-3-(2,2,2-trifluoroethylamino)-1-pyridyl]propanamide

[0001228] To a solution of 2-(3-amino-2-oxo-1-pyridyl)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (110 mg, 0.30 mmol, 1 *eq*) in DMA (1 mL) was added Na_2CO_3 (326.2 mg, 3.08 mmol, 10 *eq*) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.1 g, 9.23 mmol, 30 *eq*). The mixture was stirred at 40 °C for 16 h. TLC (DCM: MeOH = 10:1) showed new spot was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[2-oxo-3-(2,2,2-trifluoroethylamino)-1-pyridyl]propanamide (23 mg, 16.8% yield, 98.8% purity) as a white solid.

[0001229] LCMS: Rt = 0.797 min; for $C_{20}H_{24}F_3N_5O_3$ MS Calcd.: 439.18; MS Found: 440.1 [$M+H^+$].

[0001230] ^1H NMR (400 MHz, CD_3OD) δ 7.06 (dt, *J* = 1.5, 6.8 Hz, 1H), 6.65 - 6.55 (m, 1H), 6.37 - 6.27 (m, 1H), 5.56 - 5.40 (m, 1H), 5.05 - 4.98 (m, 1H), 3.88 (dq, *J* = 6.0, 9.2 Hz, 2H), 3.34 (br d, *J* = 3.0 Hz, 1H), 3.30 - 3.24 (m, 1H), 2.57 - 2.42 (m, 1H), 2.39 - 2.20 (m, 2H), 2.08 - 1.88 (m, 3H), 1.86 - 1.74 (m, 1H), 0.71 - 0.52 (m, 1H), 0.50 - 0.36 (m, 2H), 0.22 - 0.11 (m, 1H), 0.10 - 0.03 (m, 1H).

Example 145. Synthesis of viral protease inhibitor compound 467

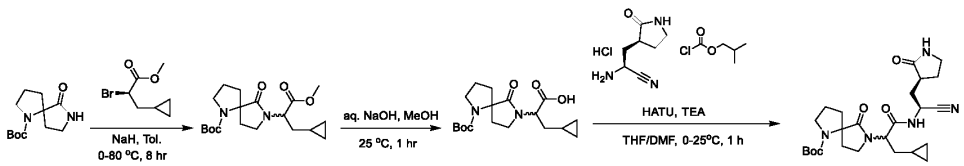


[0001231] The residue was further separated by SFC. The residue was further separated by SFC (column: DAICEL CHIRALCEL OD-H (250 mm*30 mm, 5 um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 20%-20%, min).

[0001232] Isomer 1: (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[2-oxo-3-(2,2,2-trifluoroethylamino)-1-pyridyl]propanamide (2.56 mg, 12.3% yield) as a white solid. LCMS: Rt = 0.837 min; for $C_{23}H_{31}N_5O_5$ MS Calcd.: 457.23; MS Found: 458.1 [$M+H^+$]. ^1H NMR (400 MHz, CD_3OD) δ 7.06 (dt, *J* = 1.5, 6.8 Hz, 1H), 6.65 - 6.55 (m, 1H), 6.37 - 6.27 (m, 1H), 5.56 - 5.40 (m, 1H), 5.05 - 4.98 (m, 1H), 3.88 (dq, *J* = 6.0, 9.2 Hz, 2H), 3.34 (br d, *J* = 3.0 Hz, 1H), 3.30 - 3.24 (m, 1H), 2.57 - 2.42 (m, 1H), 2.39 - 2.20 (m, 2H), 2.08 - 1.88 (m, 3H), 1.86 - 1.74 (m, 1H), 0.71 - 0.52 (m, 1H), 0.50 - 0.36 (m, 2H), 0.22 - 0.11 (m, 1H), 0.10 - 0.03 (m, 1H).

Isomer 2: Compound (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[2-oxo-3-(2,2,2-trifluoroethylamino)-1-pyridyl]propanamide (2.56 mg, 12.3% yield, 96.3% purity) as a white solid. LCMS: Rt = 0.794 min; for $C_{20}H_{24}F_3N_5O_3$ MS Calcd.: 439.18; MS Found: 440.1 [$M+H^+$]. ^1H NMR (400 MHz, CD_3OD) δ 7.04 (dd, *J* = 1.5, 7.0 Hz, 1H), 6.61 (d, *J* = 7.0 Hz, 1H), 6.32 (t, *J* = 7.2 Hz, 1H), 5.52 (t, *J* = 7.8 Hz, 1H), 5.01 (dd, *J* = 6.5, 9.3 Hz, 1H), 3.89 (q, *J* = 9.3 Hz, 2H), 3.37 - 3.32 (m, 2H), 2.55 - 2.46 (m, 1H), 2.36 (m, 1H), 2.32 - 2.24 (m, 1H), 1.99 - 1.93 (m, 2H), 1.93 - 1.87 (m, 1H), 1.87 - 1.78 (m, 1H), 0.64 - 0.54 (m, 1H), 0.46 - 0.34 (m, 2H), 0.18 - 0.09 (m, 1H), 0.07 -0.02 (m, 1H).

Example 146. Synthesis of viral protease inhibitor compound 468



Step 1: tert-Butyl 7-[(1S)-1-(cyclopropylmethyl)-2-methoxy-2-oxo-ethyl]-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate

[0001233] To a solution of tert-butyl 6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate (0.5 g, 2.08 mmol, 1 eq) in toluene (7 mL) was added NaH (124.8 mg, 3.12 mmol, 60% purity, 1.5 eq) at 0°C. After stirring at 25°C for 1h, methyl (R)-2-bromo-3-cyclopropylpropanoate (517.0 mg, 2.50 mmol, 1.2 eq) was added at 0°C and the mixture

was stirred at 80°C for 8 h. The reaction mixture was quenched by addition H_2O (15 mL) and extracted with EtOAc (15 mL * 3). The combined organic layers were washed with brine (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 7-(3-cyclopropyl-1-methoxy-1-oxopropan-2-yl)-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate (600 mg, crude) as a colorless oil.

Step 2: 2-(1-tert-butoxycarbonyl-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl)-3-cyclopropyl-propanoic acid

[0001234] To a solution of 2 (450.0 mg, 1.23 mmol, 1 eq) in H_2O (1 mL) and MeOH (3 mL) was added NaOH (196.4 mg, 4.91 mmol, 4 eq). The mixture was stirred at 25 °C for 1h. LC-MS showed 2 was consumed completely and 66% of desired compound was detected. The reaction mixture was quenched by addition H_2O (15 mL). The pH of the mixture was adjusted whit HCl (2 M) to 5-6. And then the mixture extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, and 2-(1-*tert*-butoxycarbonyl-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl)-3-cyclopropyl-propanoic acid (0.4 g, crude) was obtained as a colorless oil.

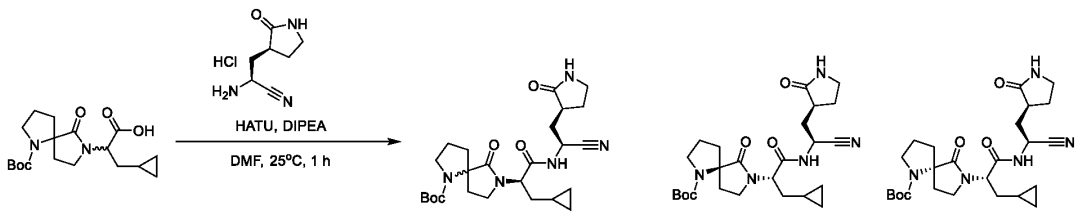
468: tert-butyl 7-[2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclo propylmethyl)-2-oxo-ethyl]-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate

[0001235] To a solution of 2-(1-*tert*-butoxycarbonyl-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl)-3-cyclopropyl-propanoic acid (50.0 mg, 0.14 mmol, 1 eq) and in THF (1 mL) was added Et_3N (14.3 mg, 0.14 mmol, 19.7 uL, 1.0 eq) and isobutyl carbonochloridate (21.3 mg, 0.15 mmol, 20.4 uL, 1.1 eq) at 0°C. The mixture was stirred at 25 °C for 1 h. A solution of (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanenitrile (32.2 mg, 0.17 mmol, 1.2 eq, HCl) and Et_3N (15.7 mg, 0.15 mmol, 21.7 uL, 1.1 eq) in DMF (1 mL) was added and the mixture was stirred at 25 °C for 1h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH4HCO3)-ACN]; B%: 23%-53%, 9.5 min) to give 468 (9.02 mg, 13% yield) as a white solid.

[0001236] LCMS: Rt = 0.821 min; for $C_{25}H_{37}N_5O_5$ MS Calcd.: 487.28; MS Found: 388.1 [M-Boc+H^+].

[0001237] ^{1}H NMR (400MHz, CD_3OD) δ 8.34 - 8.15 (m, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 5.29 - 4.98 (m, 1H), 4.95 - 4.81 (m, 1H), 3.59 - 3.47 (m, 2H), 3.46 - 3.19 (m, 4H), 2.64 - 2.29 (m, 4H), 2.28 - 2.16 (m, 1H), 2.10 - 2.00 (m, 2H), 1.97 - 1.84 (m, 4H), 1.73 - 1.60 (m, 2H), 1.53 - 1.38 (m, 9H), 0.71 - 0.52 (m, 1H), 0.51 - 0.38 (m, 2H), 0.17 - 0.07 (m, 2H).

Example 147. Synthesis of viral protease inhibitor compound 469



[0001238] Isomer 1 & Isomer 2: tert-butyl 7-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate; Isomer 3: *tert*-butyl (5*R*)-7-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate; Isomer 3: *tert*-butyl (5*S*)-7-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylate

[0001239] To a solution of 2-(1-(tert-butoxycarbonyl)-6-oxo-1,7-diazaspiro[4.4]nonan-7-yl)-3-cyclopropylpropanoic acid (200 mg, 0.56 mmol, 1 eq) and in DMF (2 mL) was added HATU (431.5 mg, 1.13 mmol, 2.0 eq), (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanenitrile (129.1 mg, 0.68 mmol, 1.2 eq, HCl) and DIPEA (146.6 mg, 1.13 mmol, 197.7 uL, 2.0 eq). The mixture was stirred at 25°C for 0.5h. TLC (Dichloromethane: Methanol=10/1, PMA) indicated reactant 1 was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol=100/1 to 10/1) to give compound 469 (150 mg) as a white solid. compound

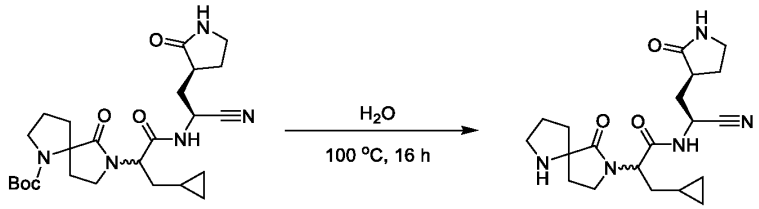
469 (150 mg) was purified by prep-HPLC column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 25%-55%, 9.5 min) to give compound 469 (60 mg) as a white solid. Compound 469 (60 mg) was purified by prep-SFC (column: DAICEL CHIRALPAK IC(250 mm*30 mm, 10 um);mobile phase: [0.1% NH_3H_2O ETOH];B%: 55%-55%, min) to Isomer 1 & Isomer 2 (15 mg, 30.7 umol, 5.42% yield), Isomer 3 (8.46 mg, 16.3 umol, 2% yield, 94% purity) Isomer 4 (9.97 mg, 18.2 umol, 3% yield, 89% purity) as three white solids.

[0001240] Isomer 1 & 2: LCMS: Rt = 1.610 for $C_{25}H_{37}N_5O_5$ MS Calcd.: 487.28; MS Found: 488.2 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 5.20 - 4.98 (m, 1H), 4.81 - 4.71 (m, 1H), 3.61 - 3.41 (m, 3H), 3.38 - 3.32 (m, 3H), 2.61 - 2.41 (m, 2H), 2.40 - 2.19 (m, 2H), 2.18 - 1.66 (m, 9H), 1.52 - 1.33 (m, 9H), 0.78 - 0.57 (m, 1H), 0.56 - 0.38 (m, 2H), 0.25 - 0.04 (m, 2H).

[0001241] Isomer 3: LCMS: Rt = 1.631 for $C_{25}H_{37}N_5O_5$ MS Calcd.: 487.28; MS Found: 488.2 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 5.20 - 4.97 (m, 1H), 4.53 - 4.32 (m, 1H), 3.64 - 3.41 (m, 3H), 3.31 (s, 3H), 2.63 - 2.35 (m, 2H), 2.35 - 2.12 (m, 2H), 2.12 - 1.74 (m, 8H), 1.73 - 1.52 (m, 1H), 1.73 - 1.52 (m, 1H), 1.50 - 1.35 (m, 9H), 0.75 (s, 1H), 0.62 - 0.36 (m, 2H), 0.24 - 0.07 (m, 2H).

[0001242] Isomer 4: LCMS: Rt = 1.630 for $C_{25}H_{37}N_5O_5$ MS Calcd.: 487.28; MS Found: 488.2 [M+H$^+$]. ^{1}H NMR (400MHz, CD_3OD) δ 5.23 - 5.01 (m, 1H), 4.81 - 4.74 (m, 1H), 3.64 - 3.37 (m, 3H), 3.35 (s, 3H), 2.67 - 2.42 (m, 2H), 2.42 - 2.10 (m, 3H), 2.10 - 1.68 (m, 8H), 1.54 - 1.39 (m, 9H), 0.68 - 0.57 (m, 1H), 0.55 - 0.39 (m, 2H), 0.24 - 0.05 (m, 2H).

Example 148. Synthesis of viral protease inhibitor compound 471



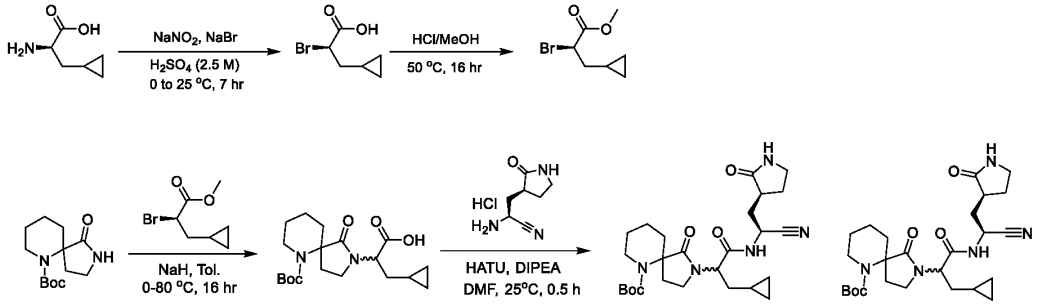
[0001243] A solution of tert-butyl 7-(1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-oxo-1,7-diazaspiro[4.4]nonane-1-

carboxylate (90 mg, 0.18 mmol, 1 eq) in H2O (4 mL) was stirred at 100 °C for 16 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 11%-41%, 9.5 min) to give N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(6-oxo-1,7-diazaspiro[4.4]nonan-7-yl)propanamide (2.41 mg, 6.10 umol, 3% yield, 98% purity) as a white solid.

[0001244] LCMS: Rt = 0.603 min; for $C_{20}H_{29}N_5O_3$ MS Calcd.: 387.23; MS Found: 388.1 [$M+H^+$].

[0001245] ^{1}H NMR (400 MHz, CD_3OD) δ 5.01 (dd, *J* = 6.3, 9.8 Hz, 1H), 4.55 (s, 1H), 3.57 - 3.47 (m, 2H), 3.37 - 3.32 (m, 2H), 3.18 - 3.08 (m, 1H), 2.99 - 2.87 (m, 1H), 2.61 - 2.48 (m, 1H), 2.34 - 2.24 (m, 2H), 2.13 - 2.00 (m, 2H), 1.93 - 1.80 (m, 7H), 1.65 - 1.56 (m, 1H), 0.75 - 0.63 (m, 1H), 0.56 - 0.45 (m, 2H), 0.17 (d, *J* = 3.5 Hz, 2H).

Example 149. Synthesis of viral protease inhibitor compound 473



Step 1: (2R)-2-bromo-3-cyclopropyl-propanoic acid

[0001246] To a solution of (2*R*)-2-amino-3-cyclopropyl-propanoic acid (3.5 g, 27.10 mmol, 1 *eq*) and NaBr (9.76 g, 94.85 mmol, 3.05 mL, 3.5 *eq*) in a 2.5 M solution of H_2SO_4 (35 mL) was added $NaNO_2$ (2.43 g, 35.23 mmol, 1.3 *eq*) in H_2O (7 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and 25 °C for 6 h. The mixture was diluted with water (60 mL) and the resultant mixture was extracted with DCM (80 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure to give (2*R*)-2-bromo-3-cyclopropyl-propanoic acid (7.4 g, crude) as colorless oil.

[0001247] ^{1}H NMR (400MHz, $CDCl_3$) δ 4.33 (t, *J*=7.4 Hz, 1H), 1.99 (dt, *J*=2.1, 7.1 Hz, 2H), 0.91 - 0.79 (m, 1H), 0.58 - 0.51 (m, 2H), 0.22 - 0.15 (m, 2H).

Step 2: Methyl (2R)-2-bromo-3-cyclopropyl-propanoate

[0001248] To a solution of (2*R*)-2-bromo-3-cyclopropyl-propanoic acid (7.4 g, 38.33 mmol, 1 *eq*) in MeOH (70 mL) was added HCl (12 M, 7.40 mL, 2.32 *eq*), and then the reaction mixture was stirred at 50 °C for 16 h. TLC (Petroleum ether : Ethyl acetate = 10:1, PMA) showed the starting material was consumed. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with ethyl acetate (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel (petroleum ether: ethyl acetate = 1:0 to 10:1) to afford methyl (2*R*)-2-bromo-3-cyclopropyl-propanoate (4.9 g, 59.2% yield) as colorless oil.

[0001249] ^{1}H NMR (400MHz, $CDCl_3$) δ 4.31 (t, *J*=7.4 Hz, 1H), 3.80 (s, 3H), 2.00 - 1.94 (m, 2H), 0.86 - 0.75 (m, 1H), 0.57 - 0.44 (m, 2H), 0.22 - 0.09 (m, 2H).

Step 3: 2-(6-tert-butoxycarbonyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl)-3-cyclopropyl-propanoic acid

[0001250] To a solution of *tert*-butyl 1-oxo-2,6-diazaspiro[4.5]decane-6-carboxylate (500 mg, 1.97 mmol, 1 *eq*) in Toluene (10 mL) was added NaH (94.37 mg, 2.36 mmol, 60% purity, 1.2 *eq*) at 0 °C, and then the mixture was stirred for 0.5 h at 25 °C. The reaction mixture was cooled to 0 °C. Methyl (2*R*)-2-bromo-3-cyclopropyl-propanoate (488.5 mg, 2.36 mmol, 1.2 *eq*) was added, and the reaction mixture was allowed to warm up to 80 °C and stirred for 16 h at 80 °C. LC-MS showed starting material was consumed completely and one main peak with desired MS was detected. TLC (petroleum ether: ethyl acetate = 1:1, PMA) showed the starting material was consumed. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with ethyl acetate (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure to give tert-butyl 2-[1-(cyclopropylmethyl)-2-methoxy-2-oxo-ethyl]-1-oxo-2,6-diazaspiro[4.5]decane-6-carboxylate (480 mg, crude) as light yellow oil.
The aqueous was acidified with HCl (0.5 N) to pH = 5, and the resultant mixture

was extracted with ethyl acetate (20 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure to give 2-(6-tert-butoxycarbonyl-1-oxo-2,6-diazaspiro[4.5]decan-2-yl)-3-cyclopropyl-propanoic acid (120 mg, crude) as light yellow oil.

[0001251] Isomer 1: *tert*-butyl 2-[2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1-oxo-2,6-diazaspiro[4.5]decane-6-carboxylate; Isomer 2: *tert*-butyl 2-[2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1-oxo-2,6-diazaspiro[4.5]decane-6-carboxylate

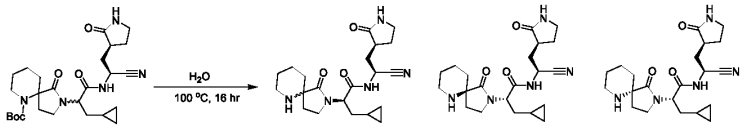
[0001252] To a solution of 2-(6-(tert-butoxycarbonyl)-1-oxo-2,6-diazaspiro[4.5]decan-2-yl)-3-cyclopropylpropanoic acid (0.1 g, 0.27 mmol, 1 eq) in DMF (1 mL) was added HATU (207.5 mg, 0.54 mmol, 2.0 eq), (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanenitrile hydrochloride (62.1 mg, 0.32 mmol, 1.2 eq, HCl) and DIPEA (52.9 mg, 0.40 mmol, 71.3 uL, 1.5 eq). The mixture was stirred at 25°C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 27%-57%, 9.5 min) to give Isomer 1 (18.9 mg, 13% yield) and Isomer 2 (2.54 mg, 1.8% yield) as two white solids.

[0001253] Isomer 1: LCMS: Rt = 0.831 min; for $C_{26}H_{39}N_5O_5$ MS Calcd.: 501.30; MS Found: 502.2 [$M+H^+$]. ^1H NMR (400 MHz, CD_3OD) δ 5.20 - 5.01 (m, 1H), 4.81 - 4.68 (m, 1H), 3.90 (td, *J* = 4.6, 8.6 Hz, 1H), 3.59 - 3.40 (m, 1H), 3.34 (d, *J* = 3.3 Hz, 3H), 3.07 - 2.85 (m, 1H), 2.64 - 2.45 (m, 1H), 2.45 - 2.22 (m, 3H), 2.21 - 2.07 (m, 1H), 2.05 - 1.92 (m, 1H), 1.90 - 1.62 (m, 7H), 1.57 (d, *J* = 10.5 Hz, 2H), 1.51 - 1.39 (m, 9H), 0.81 - 0.57 (m, 1H), 0.55 - 0.33 (m, 2H), 0.22 - 0.04 (m, 2H).

[0001254] Isomer 2: LCMS: Rt = 0.845 min; for $C_{26}H_{39}N_5O_5$ MS Calcd.: 501.30; MS Found: 502.2 [$M+H^+$]. ^1H NMR (400 MHz, CD_3OD) δ 5.28 - 5.14 (m, 1H), 5.28 - 5.14 (m, 1H), 4.77 (t, *J* = 7.7 Hz, 1H), 3.93 (br d, *J* = 13.1 Hz, 1H), 3.51 - 3.38 (m, 1H), 3.35 - 3.31 (m, 1H), 3.35 - 3.31 (m, 2H), 3.06 - 2.92 (m, 1H), 2.61 - 2.48 (m, 1H), 2.45 - 2.22

(m, 3H), 2.19 - 2.08 (m, 1H), 1.97 (td, *J* = 8.2, 13.7 Hz, 1H), 1.89 - 1.65 (m, 7H), 1.64 - 1.52 (m, 2H), 1.49 (s, 9H), 0.64 - 0.54 (m, 1H), 0.53 - 0.30 (m, 2H), 0.22 - 0.00 (m, 2H).

Example 150. Synthesis of viral protease inhibitor compound 475



[0001255] Isomer 1 & Isomer 2: (2*R*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(1-oxo-2,6-diazaspiro[4.5]decan-2-yl)propenamide; Isomer 3: (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*R*)-1-oxo-2,6-diazaspiro[4.5]decan-2-yl]propenamide; Isomer 4: (2*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-[(5*S*)-1-oxo-2,6-diazaspiro[4.5]decan-2-yl]propanamide

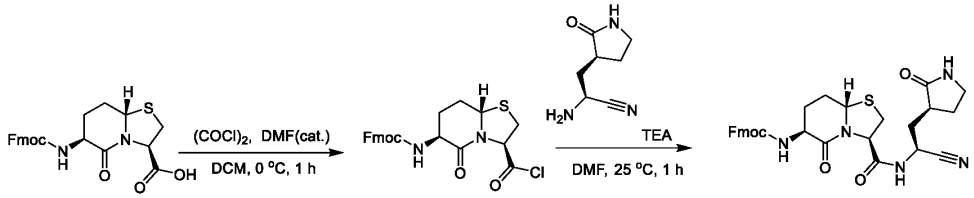
[0001256] A solution of *tert*-butyl 2-(1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1-oxo-2,6-diazaspiro[4.5]decane-6-carboxylate (0.15 g, 0.29 mmol, 1 eq) in H_2O (5 mL) was stirred at 100°C for 16 h . The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 1%-31%, 9.5 min) to give 475 Isomer 1 & Isomer 2 (6.00 mg, 5% yield) and 475 Isomer 3 & Isomer 4 (24.65 mg) as two white solids. 475 Isomer 3 & Isomer 4 was purified by prep-SFC (column: DAICEL CHIRALPAK AD(250 mm*30 mm,10 um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 40%-40%, min) to give 475 Isomer 3 (5.53 mg, 4% yield) and 475 Isomer 4 (4.84 mg, 3% yield) as two white solids.

[0001257] 475 Isomer 1 & Isomer 2: LCMS： Rt = 1.232 min; for $C_{21}H_{31}N_5O_3$ MS Calcd.: 401.24; MS Found: 402.1 [$M+H^+$]. ^1H NMR (400 MHz, CD_3OD) δ 5.04 - 4.92 (m, 1H), 4.67 - 4.60 (m, 1H), 3.73 - 3.39 (m, 2H), 3.37 - 3.32 (m, 2H), 3.15 - 3.00 (m, 1H), 2.88 (d, *J* = 6.5 Hz, 1H), 2.62 - 2.42 (m, 1H), 2.40 - 2.15 (m, 6H), 2.11 - 1.76 (m, 8H), 1.68 - 1.51 (m, 1H), 0.75 - 0.57 (m, 1H), 0.57 - 0.39 (m, 2H), 0.23 - 0.11 (m, 2H).

[0001258] Isomer 3: LCMS: Rt = 1.332 min; for $C_{21}H_{31}N_5O_3$ MS Calcd.: 401.24; MS Found: 402.2 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 4.90 - 4.82 (m, 1H), 4.47 (dd, *J* = 6.5, 9.0 Hz, 1H), 3.46 - 3.34 (m, 1H), 3.31 - 3.23 (m, 1H), 3.20 - 3.15 (m, 3H), 3.02 - 2.89 (m, 1H), 2.64 - 2.48 (m, 1H), 2.43 - 2.32 (m, 1H), 2.27 - 2.01 (m, 3H), 1.92 - 1.65 (m, 5H), 1.55 - 1.39 (m, 5H), 0.53 - 0.41 (m, 1H), 0.39 - 0.23 (m, 2H), 0.07 - -0.08 (m, 2H).

[0001259] Isomer 4: LCMS: Rt = 1.329 min; for $C_{21}H_{31}N_5O_3$ MS Calcd.: 401.24; MS Found: 402.2 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 4.96 (d, *J* = 3.0 Hz, 1H), 4.66 (dd, *J* = 6.0, 9.5 Hz, 1H), 3.65 - 3.56 (m, 1H), 3.49 - 3.40 (m, 1H), 3.37 - 3.32 (m, 3H), 3.20 - 3.09 (m, 1H), 2.82 - 2.69 (m, 1H), 2.50 (td, *J* = 8.1, 16.3 Hz, 1H), 2.41 - 2.31 (m, 2H), 2.25 (ddd, *J* = 6.3, 9.5, 13.9 Hz, 1H), 2.10 (td, *J* = 9.0, 12.6 Hz, 1H), 2.01 - 1.79 (m, 4H), 1.71 - 1.57 (m, 5H), 0.65 - 0.55 (m, 1H), 0.54 - 0.37 (m, 2H), 0.21 - 0.08 (m, 2H).

Example 151. Synthesis of viral protease inhibitor compound 477



Step 1: (9H-fluoren-9-yl)methyl((3S,6S,8aS)-3-(chlorocarbonyl)-5-oxohexahydro-2H-thiazolo[3,2-a]pyridin-6-yl)carbamate

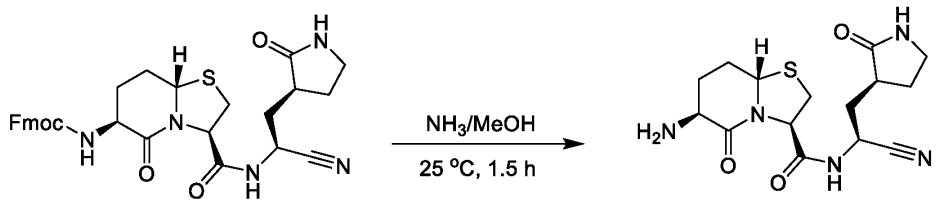
[0001260] To a solution of (3R,6S)-6-(9H-fluoren-9-ylmethoxycarbonylamino)-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridine-3-carboxylic acid (200 mg, 0.45 mmol, 1 *eq*) in DCM (4 mL) was added $(COCl)_2$ (86.8 mg, 0.68 mmol, 59 uL, 1.5 *eq*) and DMF (3.3 mg, 45.6 umol, 3 uL, 0.1 *eq*) at 0°C under N_2. The mixture was stirred at 0 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. It was used into next step without purification. Compound 9H-fluoren-9-ylmethylN-[(3S,6S)-3-chlorocarbonyl-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridin-6-yl]carbamate (200 mg, crude) was obtained as a yellow solid.

(9H-fluoren-9-yl)methyl((3R,6S,8aS)-3-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)carbamoyl)-5-oxohexahydro-2H-thiazolo[3,2-a]pyridin-6-yl)carbamate

[0001261] To a solution of 9H-fluoren-9-ylmethyl N-[(3S,6S)-3-chlorocarbonyl-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridin-6-yl]carbamate (200 mg, 0.43 mmol, 1 *eq*) in DMF (5 mL) was added TEA (132.8 mg, 1.31 mmol, 0.18 mL, 3 *eq*) and (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanenitrile (99.6 mg, 0.52 mmol, 1.2 *eq*, HCl). The mixture was stirred at 25 °C for 1 hr. TLC (petroleum ether/ethyl acetate = 0:1, UV 254). The reaction mixture was added with H_2O (10 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ethergradient @ 30 mL/min) to give a yellow solid. The residue purified by prep-HPLC (column: 3_Phenomenex Luna C18 75*30 mm*3 um; mobile phase: [water(0.05% HCl)-ACN];B%: 30%-60%,8.5 min). Compound 9H-fluoren-9-ylmethyl N-[(3R,6S)-3-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridin-6-yl]carbamate (10.63 mg, 18.4 umol, 4.2% yield, 99.7% purity) was obtained as a white solid. LCMS： Rt = 0.834 min; for $C_{30}H_{31}N_5O_5S$ MS Calcd.: 573.66; MS Found: 574.2 [$M+H^+$].

[0001262] ^1H NMR (400 MHz, CD_3OD) δ 7.82 (d, *J* = 7.53 Hz, 2 H), 7.65 - 7.72 (m, 2 H), 7.37 - 7.45 (m, 2 H), 7.29 - 7.36 (m, 2 H), 5.02 - 5.11 (m, 3 H), 4.43 (d, *J* = 6.78 Hz, 2 H), 4.23 - 4.30 (m, 1 H), 4.01 (br dd, *J* = 11.29, 6.78 Hz, 1 H), 3.42 (dd, *J* = 11.54, 7.78 Hz, 1 H), 3.19 - 3.30 (m, 3 H), 2.52 - 2.65 (m, 1 H), 2.17 - 2.43 (m, 4 H), 2.03 - 2.13 (m, 1 H), 1.84 - 1.97 (m, 2 H), 1.73 - 1.83 (m, 1 H).

Example 152. Synthesis of viral protease inhibitor compound 479



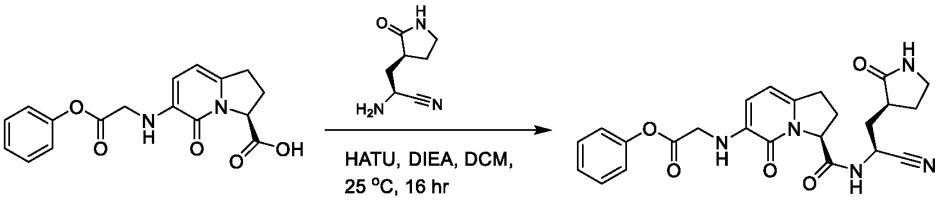
[0001263] To a solution of 9H-fluoren-9-ylmethyl N-[(3R,6S)-3-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridin-6-yl]carbamate (100 mg, 0.17 mmol, 1 *eq*) in MeOH (0.1 mL) was added NH_3 (7 M, 2.00

mL, 80.31 *eq*). The mixture was stirred at 25 °C for 1.5 h. The reaction mixture was added H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The aqueous phase were concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 0%-23%,7.8 min). Compound (3R,6S)-6-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5-oxo-2,3,6,7,8,8a-hexahydrothiazolo[3,2-a]pyridine-3-carboxamide (16.59 mg, 47.2 umol, 27.0% yield, 100% purity) was obtained as a white solid.

[0001264] LCMS: Rt = 1.495 min; for $C_{15}H_{21}N_5O_3S$ MS Calcd.: 351.42; MS Found: 352.1 [$M+H^+$].

[0001265] ^1H NMR (400 MHz, CD_3OD) δ ppm 4.99 (br dd, J = 10.63, 5.63 Hz, 3 H), 3.33 - 3.45 (m, 4 H), 3.14 - 3.25 (m, 1 H), 2.58 - 2.71 (m, 1 H), 2.19 - 2.44 (m, 4 H), 1.75 - 2.00 (m, 4 H).

Example 153. Synthesis of viral protease inhibitor compound 483



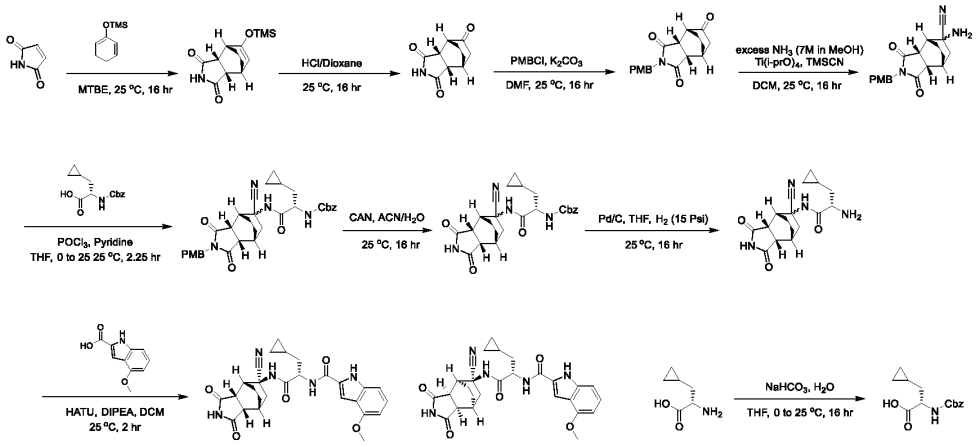
[0001266] To a solution of (3S)-5-oxo-6-[(2-oxo-2-phenoxy-ethyl)amino]-2,3-dihydro-1*H*-indolizine-3-carboxylic acid (100 mg, 0.30 mmol, 1 *eq*) in DCM (3 mL) was added HATU (138.9 mg, 0.36 mmol, 1.2 *eq*) and DIPEA (118.0 mg, 0.91 mmol, 0.15 mL, 3 *eq*) for 1 h. Then, (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanenitrile (55.9 mg, 0.29 mmol, 9.69e-1 *eq*, HCl) was added into the mixture, and the resulting mixture was stirred at 25 °C for 15 h. TLC (DCM/MeOH = 10:1). The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic phase was washed with brine (5 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH ethergradient @ 20 mL/min) to give phenyl 2-[[(3*S*)-3-[[(1*S*)-1-cyano-2-[(3*S*)-2-

oxopyrrolidin-3-yl]ethyl]carbamoyl]-5-oxo-2,3-dihydro-1*H*-indolizin-6-yl]amino]acetate (35 mg, 75.3 umol, 24.7% yield, 99.8% purity) as a white solid.

[0001267] LCMS: Rt = 0.770 min; for $C_{24}H_{25}N_5O_5$ MS Calcd.: 463.19; MS Found: 464.1 [$M+H^+$].

[0001268] ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (br s, 1H), 7.46 - 7.24 (m, 5H), 6.32 (br d, *J* = 7.6 Hz, 1H), 5.19 (s, 2H), 5.10 - 4.99 (m, 3H), 3.34 (br d, *J* = 3.3 Hz, 1H), 3.24 - 3.06 (m, 2H), 2.74 - 2.63 (m, 1H), 2.62 - 2.45 (m, 2H), 2.40 - 2.23 (m, 3H), 1.97 - 1.80 (m, 2H).

Example 154. Synthesis of viral protease inhibitor compound 489



Step 1: (1R,2S,6R,7R)-8-trimethylsilyloxy-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione

[0001269] A solution of cyclohexa-1,5-dien-1-yloxy(trimethyl)silane (5.0 g, 29.71 mmol, 5.50 mL, 1 *eq*) and pyrrole-2,5-dione (2.88 g, 29.71 mmol, 1 *eq*) in MTBE (50 mL) was stirred at 25 °C for 16 h. TLC (petroleum ether : ethyl acetate = 2:1, I_2) was conducted. The reaction mixture was concentrated under reduced pressure. MTBA (15 mL) and PE (15 mL) was added, and then the suspension was filtered to give the title compound as a white solid. Compound (1R,2S,6R,7R)-8-trimethylsilyloxy-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (5.2 g, 65.9% yield) was obtained as a white solid

Step 2: (1R,2S,6R,7R)-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione

[0001270] A solution of (1R,2S,6R,7R)-8-trimethylsilyloxy-4-azatricyclo[5.2.2.$0^{2,6}$]undec-8-ene-3,5-dione (2.9 g, 10.93 mmol, 1 *eq*) in HCl/dioxane (25 mL) was stirred at 25 °C for 16 hr. TLC (petroleum ether: ethyl acetate = 5:1). The reaction mixture was concentrated in vacuum. No purification. The crude product was used into the next step without further purification. Compound (1R,2S,6R,7R)-4-azatricyclo[5.2.2.$0^{2,6}$]undecane-3,5,8-trione (2.16 g, crude) was obtained as a white solid.

Step 3: (1R,2S,6R,7R)-4-[(4-methoxyphenyl)methyl]-4-azatricyclo[5.2.2.$0^{2,6}$]undecane-3,5,8-trione

[0001271] To a solution of (1*R*,2*S*,6*R*,7*R*)-4-azatricyclo[5.2.2.$0^{2,6}$]undecane-3,5,8-trione (2.1 g, 11.18 mmol, 1 *eq*) in DMF (20 mL) was added PMBCl (2.1 g, 13.42 mmol, 1.83 mL, 1.2 *eq*) and K_2CO_3 (2.3 g, 16.77 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 16 h. LCMS showed the desired compound was detected. TLC (petroleum ether: ethyl acetate = 1:1). The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% petroleum ether/ethyl acetate ethergradient @ 25 mL/min). Compound (1*R*,2*S*,6*R*,7*R*)-4-[(4-methoxyphenyl)methyl]-4-azatricyclo[5.2.2.$0^{2,6}$]undecane-3,5,8-trione (3.03 g, 86.4% yield) was obtained as a white solid.

Step 4: (1R,2S,6R,7R)-8-Amino-4-[(4-methoxyphenyl)methyl]-3,5-dioxo-4-azatricyclo[5.2.2.$0^{2,6}$]undecane-8-carbonitrile

[0001272] To a solution of (1*R*,2*S*,6*R*,7*R*)-4-[(4-methoxyphenyl)methyl]-4-azatricyclo[5.2.2.$0^{2,6}$]undecane-3,5,8-trione (1.7 g, 5.43 mmol, 1 *eq*) in DCM (25 mL) were added NH_3 (7 M, 7.75 mL, 10 *eq*) and Ti(i-PrO)$_4$ (1.85 g, 6.51 mmol, 1.92 mL, 1.2 *eq*). The reaction mixture was stirred at 25 °C for 2 hr. TMSCN (807.3 mg, 8.14 mmol, 1.02 mL, 1.5 *eq*) was added and the solution was stirred at 25 °C for 16 h. Ethyl acetate (100 mL) and H_2O (10 mL) were added, the reaction mixture was filtered, the filtrate was concentrated to reduce pressure. Compound (1*R*,2*S*,6*R*,7*R*)-8-amino-4-[(4-methoxyphenyl)methyl]-3,5-dioxo-4-azatricyclo[5.2.2.$0^{2,6}$]undecane-8-carbonitrile (1.75 g, crude) was obtained as a white solid.

Step 5: (2S)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoic acid

[0001273] To a solution of (2*S*)-2-amino-3-cyclopropyl-propanoic acid (3.0 g, 23.23 mmol, 1 *eq*) in THF (45 mL) was added Na_2CO_3 (2 M, 13.94 mL, 1.2 *eq*) at 0 °C. CbzCl (5.15 g, 30.20 mmol, 4.29 mL, 1.3 *eq*) was added, and the reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (30 mL) and the resultant mixture was extracted with ethyl acetate (50 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel (petroleum ether: ethyl acetate = 1:0 to 3:1) to afford (2*S*)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoic acid as a colorless oil. Compound (2*S*)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoic acid (3.2 g, 10.21 mmol, 43.9% yield, 84% purity) was obtained as colorless oil. ^{1}H NMR (400MHz, CD_3OD) δ 7.43 - 7.20 (m, 5H), 5.09 (s, 2H), 4.23 (dd, *J* = 5.5, 8.0 Hz, 1H), 1.73 - 1.58 (m, 2H), 0.86 - 0.72 (m, 1H), 0.53 - 0.39 (m, 2H), 0.20 - 0.02 (m, 2H).

Step 6: Benzyl N-[(1S)-2-[[(1R,2S,6R,7R)-8-cyano-4-[(4-methoxyphenyl)methyl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate

[0001274] A solution of (1*R*,2*S*,6*R*,7*R*)-8-amino-4-[(4-methoxyphenyl)methyl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecane-8-carbonitrile (1.7 g, 5.01 mmol, 1 *eq*), (2S)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoic acid (1.45 g, 5.51 mmol, 1.1 *eq*) and pyridine (3.96 g, 50.09 mmol, 4.04 mL, 10 *eq*) in THF (35 mL) was stirred at 25 °C for 15 min. After $POCl_3$ (1.92 g, 12.52 mmol, 1.16 mL, 2.5 *eq*) was added dropwise at 0 °C, the reaction mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (30 mL) and the resultant mixture was extracted with ethyl acetate (80 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel (DCM: MeOH = 1:0 to 20:1) to afford *N*-[(1*S*)-2-[[(1*R*,2*S*,6*R*,7*R*)-8-cyano-4-[(4-methoxyphenyl)methyl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (2.4 g, 72.9% yield, 89% purity) as a colorless oil.

Step 7: Benzyl N-[(1S)-2-[[(1R,2S,6R,7R)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]

[0001275] To a solution of benzyl *N*-[(1*S*)-2-[[(1*R*,2*S*,6*R*,7*R*)-8-cyano-4-[(4-methoxyphenyl)methyl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (500 mg,0. 85 mmol, 1 *eq*) in ACN (15 mL) and H_2O (5 mL) was added CAN (1.41 g, 2.57 mmol, 1.28 mL, 3 *eq*), and then the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (30 mL) and the resultant mixture was extracted with ethyl acetate (50 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel (petroleum ether:ethyl acetate = 1:0 to 1:1) to afford benzyl *N*-[(1*S*)-2-[[(1*R*,2*S*,6*R*,7*R*)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (260 mg, 62.8% yield, 96% purity) as a white solid.

Step 8: (2S)-2-amino-N-[(1R,2S,6R,7R)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]-3-cyclopropyl-propanamide

[0001276] To a solution of benzyl *N*-[(1*S*)-2-[[(1*R*,2*S*,6*R*,7*R*)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (200 mg, 0.43 mmol, 1 *eq*) in THF (2 mL) was added Pd/C (100 mg, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) 25 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under pressure reduce. Compound (2*S*)-2-amino-*N*-[(1*R*,2*S*,6*R*,7*R*)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]-3-cyclopropyl-propanamide (140 mg, crude) was obtained as colorless oil.

[0001277] Isomer 1: *N*-[(1*S*)-2-[[(1*R*,2*S*,6*R*,7*R*,8*S*)-8-Cyano-3,5-dioxo-4-azatricyclo[5.2.2.02,6]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide; Isomer 2: *N*-[(1*S*)-2-[[(1*S*,2*R*,6*S*,7*S*,8*S*)-8-Cyano-3,5-dioxo-4-azatricyclo[5.2.2.02,6]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide

[0001278] To a solution of (2*S*)-2-amino-*N*-[(1*R*,2*S*,6*R*,7*R*)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]-3-cyclopropyl-propanamide (140 mg, 0.42 mmol, 1 *eq*), 4-methoxy-1*H*-indole-2-carboxylic acid (81.01 mg, 0.42 mmol, 1 *eq*) and DIPEA

(109.5 mg, 0.84 mmol, 147.62 uL, 2 *eq*) in DCM (4 mL) was added HATU (193.3 mg, 0.50 mmol, 1.2 *eq*). The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (10 mL) and the resultant mixture was extracted with DCM (20 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by *Pre*-TLC (DCM: MeOH =10:1) to give the crude product. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 23%-53%, 9.5 min) to give Isomer 1 (13.30 mg, 6.0% yield, 97.4% purity) and Isomer 2 (31.40 mg, 14.6% yield, 99.5% purity) as two white solids.

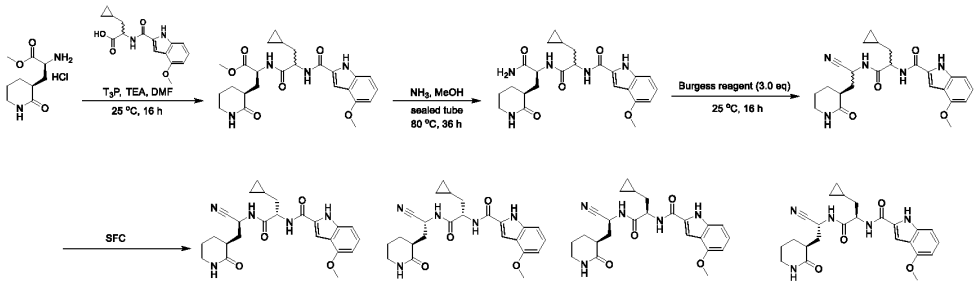
[0001279] Isomer 1: LCMS: Rt = 0.808 min; for $C_{27}H_{29}N_5O_5$ MS Calcd.: 503.22; MS Found: 504.2 [$M+H^+$].

[0001280] ^1H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1H), 7.18 - 7.12 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 4.56 (dd, *J* = 4.4, 9.9 Hz, 1H), 3.93 (s, 3H), 3.17 (d, *J* = 2.5 Hz, 1H), 3.02 - 2.97 (m, 1H), 2.96 - 2.90 (m, 1H), 2.41 (d, *J* = 15.3 Hz, 1H), 2.33 (d, *J* = 2.3 Hz, 1H), 2.22 - 2.10 (m, 1H), 1.94 (d, *J* = 15.3 Hz, 1H), 1.88 - 1.63 (m, 5H), 0.90 - 0.75 (m, 1H), 0.56 - 0.40 (m, 2H), 0.31 - 0.13 (m, 2H).

[0001281] Isomer 2: LCMS: Rt = 0.806 min; for $C_{27}H_{29}N_5O_5$ MS Calcd.: 503.22; MS Found: 504.2 [$M+H^+$].

[0001282] ^1H NMR (400MHz, CD_3OD) δ 7.25 (s, 1H), 7.18 - 7.11 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 4.64 - 4.60 (m, 1H), 3.93 (s, 3H), 3.17 (d, *J* = 2.0 Hz, 1H), 3.00 - 2.93 (m, 1H), 2.92 - 2.86 (m, 1H), 2.43 (d, *J* = 15.6 Hz, 1H), 2.31 (s, 1H), 2.23 - 2.11 (m, 1H), 1.94 (d, *J* = 15.6 Hz, 1H), 1.84 - 1.61 (m, 5H), 0.85 - 0.70 (m, 1H), 0.55 - 0.40 (m, 2H), 0.23 - 0.09 (m, 2H).

Example 155. Synthesis of viral protease inhibitor compound 491



Step 1: methyl (2S)-2-[[3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001283] To the mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (240 mg, 1.01 mmol, 1 *eq*, HCl), (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (412.2 mg, 1.22 mmol, 1.2 *eq*, HCl) and TEA (410.4 mg, 4.06 mmol, 0.56 mL, 4 *eq*) in DMF (3 mL) was added T_3P (1.2 g, 2.03 mmol, 1.21 mL, 50% purity, 2 *eq*) at 25 °C. The mixture was stirred at 25 °C for 16 h. TLC (DCM:MeOH =10:1/UV254nm). The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 100~25% Ethyl acetate/MeOH@ 30 mL/min). Compound methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (256 mg, 0.48 mmol, 48.2% yield, 92.5% purity) was obtained as yellow solid.

Step 2: N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[0001284] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (246.3 mg, 0.47 mmol, 92.5% purity, 1 *eq*) in NH_3 (7 M, 6.72 mL, 100 *eq*) (7M in MeOH) was stirred at 80 °C for 36 h in a sealed tube. The reaction mixture was concentrated in vacuum. Compound N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (220 mg, crude) was obtained as yellow solid, which was used into the next step without further purification.

Step 3: N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[0001285] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (250 mg, 0.53 mmol, 1 *eq*) and methoxycarbonyl-(triethylammonio)sulfonyl-azanide (444.0 mg, 1.86 mmol, 3.5 *eq*) in DCM (3 mL) was stirred at 25 °C for 16 h. LC-MS showed the desired compound was detected. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*30 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 23%-53%, 9.5 min). Compound N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (83 mg, 0.18 mmol, 34.2% yield, 99.0% purity) was obtained as a white solid.

[0001286] Isomer 1: *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide; Isomer 2: *N*-[(1*S*)-2-[[(1*R*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide; Isomer 3: *N*-[(1*R*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide; Isomer 3: *N*-[(1*R*)-2-[[(1*R*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-indole-2-carboxamide

[0001287] N-[2-[[1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (50 mg, 0.11 mmol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALPAK AD(250 mm*30 mm, 10 um);mobile phase: [0.1% NH_3H_2O ETOH];B%: 55%-55%, min) to get three fragments: Isomer 1 , mixture of Isomer 2 &3 and Isomer 4.

[0001288] Isomer 1: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (28.1 mg, 62.2 umol, 56.2% yield, 100% purity) was obtained as white solid.

[0001289] LCMS: Rt = 0.755min; for $C_{24}H_{29}N_5O_4$ MS Calcd.: 451.22, MS Found: 452.2 [M+H$^+$].

[0001290] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 8.91 (br d, *J* = 8.0 Hz, 1H), 8.50 (br d, *J* = 7.5 Hz, 1H), 7.53 (br s, 1H), 7.37 (d, *J* = 1.4 Hz, 1H), 7.15 - 7.06 (m, 1H), 7.04 - 6.97 (m, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 5.07 (q, *J* = 8.2 Hz, 1H), 4.49 - 4.40 (m, 1H), 3.89 (s, 3H), 3.15 - 3.01 (m, 2H), 2.34 - 2.20 (m, 2H), 1.91 - 1.76 (m, 3H), 1.70 (br dd, *J* = 4.4, 8.7 Hz, 1H), 1.64 - 1.53 (m, 1H), 1.35 (br s, 1H), 0.86 - 0.76 (m, 1H), 0.48 - 0.35 (m, 2H), 0.25 - 0.04 (m, 2H).

[0001291] Isomer 4: N-[(1R)-2-[[(1R)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (6.1 mg, 13.5 umol, 12.2% yield, 100% purity) was obtained as white solid.

[0001292] LCMS: Rt = 0.752min; for $C_{24}H_{29}N_5O_4$ MS Calcd.: 451.22, MS Found: 452.2 [M+H$^+$].

[0001293] ^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (s, 1H), 7.18 - 7.12 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 5.12 (dd, *J* = 6.4, 7.7 Hz, 1H), 4.85 (br s, 1H), 3.93 (s, 3H), 3.24 - 3.16 (m, 2H), 2.50 - 2.32 (m, 2H), 2.06 - 1.92 (m, 2H), 1.92 - 1.82 (m, 2H), 1.70 (dt, *J* = 7.0, 14.2 Hz, 2H), 1.63 - 1.54 (m, 1H), 1.31 - 1.31 (m, 1H), 1.41 - 1.27 (m, 1H), 0.91 - 0.80 (m, 1H), 0.53 (br d, *J* = 8.0 Hz, 2H), 0.25 - 0.14 (m, 2H).

[0001294] The mixture of Isomer 2 & Isomer 3 (20.0 mg, 44.3 umol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALCEL OD-H(250 mm*30 mm, 5um);mobile phase: [0.1% NH_3H_2O ETOH];B%: 45%-45%, min) to get two fragments.

[0001295] Isomer 3: N-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (5.1 mg, 11.3 umol, 25.6% yield, 100% purity) was obtained as white solid.

[0001296] LCMS: Rt = 0.754min; for $C_{24}H_{29}N_5O_4$ MS Calcd: 451.22, MS Found: 452.1 [M+H$^+$].

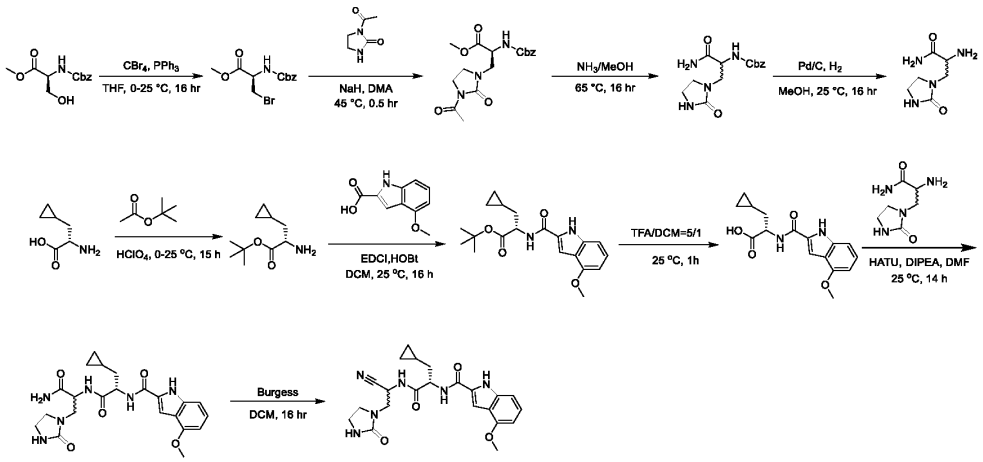
[0001297] ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1H), 7.18 - 7.12 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.06 (dd, *J* = 6.5, 9.8 Hz, 1H), 4.81 (br s, 1H), 3.93 (s, 3H), 3.18 (br s, 2H), 2.43 - 2.35 (m, 1H), 2.45 - 2.27 (m, 1H), 2.31 (br s, 1H), 2.06 - 1.95 (m, 1H), 1.94 - 1.78 (m, 3H), 1.76 - 1.59 (m, 2H), 1.58 - 1.45 (m, 1H), 1.40 (s, 1H), 1.29 (s, 1H), 0.92 - 0.79 (m, 1H), 0.58 - 0.44 (m, 2H), 0.26 - 0.12 (m, 2H).

[0001298] Isomer 2: N-[(1S)-2-[[(1R)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (6.3 mg, 14.0 umol, 31.6% yield, 100% purity) was obtained white solid.

[0001299] LCMS: Rt = 0.754min; for $C_{24}H_{29}N_5O_4$ MS Calcd: 451.22, MS Found: 452.1 [$M+H^+$].

[0001300] ^{1}H NMR (400 MHz, CD_3OD) δ 7.12 (s, 1H), 7.01 - 6.96 (m, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 4.89 (t, *J* = 7.2 Hz, 1H), 4.43 (dd, *J* = 6.3, 8.3 Hz, 2H), 3.77 (s, 3H), 3.08 - 3.00 (m, 2H), 2.32 - 2.22 (m, 1H), 2.20 - 2.10 (m, 1H), 2.27 - 2.07 (m, 1H), 1.84 - 1.73 (m, 2H), 1.72 - 1.62 (m, 2H), 1.60 - 1.50 (m, 2H), 1.43 - 1.34 (m, 1H), 0.75 - 0.62 (m, 1H), 0.40 - 0.27 (m, 2H), 0.08 - -0.04 (m, 2H).

Example 156. Synthesis of viral protease inhibitor compound 493



Step 1: Methyl (2R)-2-(benzyloxycarbonylamino)-3-bromo-propanoate

[0001301] To a solution of methyl (2*S*)-2-(benzyloxycarbonylamino)-3-hydroxy-propanoate (10 g, 39.49 mmol, 1 *eq*) and CBr_4 (15.7 g, 47.38 mmol, 1.2 *eq*) in THF (120 mL) was added PPh_3 (12.4 g, 47.38 mmol, 1.2 *eq*) in THF (20 mL) at 0 °C. Then the

mixture was stirred at 25 °C for 16 hr. TLC (petroleum ether/ethyl acetate = 5/1, I_2). The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethylacetate/Petroleum ethergradient @ 30 mL/min) to give methyl (2*R*)-2-(benzyloxycarbonylamino)-3-bromo-propanoate (8.2 g, 65.6% yield) as a white solid.

Step 2: methyl (2S)-3-(3-acetyl-2-oxo-imidazolidin-1-yl)-2-(benzyloxycarbonylamino) propanoate

[0001302] To a solution of 1-acetylimidazolidin-2-one (1.3 g, 10.31 mmol, 1 *eq*) in DMA (10 mL) was added NaH (618.6 mg, 15.47 mmol, 60% purity, 1.5 *eq*) at 25 °C and the mixture was stirred at 45 °C for 15 min. Then methyl (2*R*)-2-(benzyloxycarbonylamino)-3-bromo-propanoate (3.2 g, 10.31 mmol, 1 *eq*) in DMA (30 mL) was added to the mixture at 45 °C and the resulting mixture was stirred at 45 °C for 15 min. LC-MS showed the desired compound was detected. TLC (petroleum ether:ethyl acetate = 0:1) showed new spot was detected. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~80% petroleum ether/ethyl acetate ethergradient @ 30 mL/min). Compound methyl (2*S*)-3-(3-acetyl-2-oxo-imidazolidin-1-yl)-2-(benzyloxycarbonylamino)propanoate (1.5 g, 40.0% yield) was obtained as yellow oil.

Step 3: benzyl N-[2-amino-2-oxo-1-[(2-oxoimidazolidin-1-yl)methyl]ethyl]carbamate

[0001303] A solution of methyl 3-(3-acetyl-2-oxo-imidazolidin-1-yl)-2-(benzyloxycarbonylamino)propanoate (2.0 g, 5.50 mmol, 1 *eq*) in ammonia (7 M, 14.94 mL, 19 *eq*) was stirred at 65 °C for 16 hr. TLC (DCM:MeOH = 10:1). The reaction mixture was filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~30% DCM/MeOH ethergradient @30 mL/min). Compound benzyl *N*-[2-amino-2-oxo-1-[(2-oxoimidazolidin-1-yl)methyl]ethyl]carbamate (462 mg, 27.4% yield) was obtained as a white solid.

Step 4: 2-amino-3-(2-oxoimidazolidin-1-yl)propanamide

[0001304] To a solution of 4 (450 mg, 1.47 mmol, 1 eq) in MeOH (3 mL) was added Pd/C (0.2 g, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25°C for 1 h. TLC (dichloromethane: methanol=10/1, Ninhydrin). The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification, and 2-amino-3-(2-oxoimidazolidin-1-yl)propanamide (250 mg, crude) was obtained as a white solid.

Step 5: tert-butyl (2S)-2-amino-3-cyclopropyl-propanoate

[0001305] To a solution of 2-amino-3-(2-oxoimidazolidin-1-yl)propanamide (0.3 g, 2.3 mmol, 1 eq) in tert-butyl acetate (4.33 g, 37.2 mmol, 5 mL, 16.0 eq) was added $HClO_4$ (533.3 mg, 3.7 mmol, 0.32 mL, 70% purity, 1.6 eq) slowly at 0°C. The mixture was stirred at 25 °C for 15 h. TLC (petroleum ether: ethyl acetate=2/1, ninhydrin). The reaction mixture was diluted with H_2O (10 mL) followed by an addition of 1 N HCl (8 mL). The pH of the mixture was adjusted to about 9 with 10% aq Na_2CO_3, and then extracted with DCM (3 * 15 mL). The combined organic layers were dried over Na_2SO_4 to give tert-butyl (2S)-2-amino-3-cyclopropyl-propanoate (0.4 g, crude) as a colorless oil.

Step 6: tert-butyl (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino] propanoate

[0001306] To a solution of 4-methoxy-1H-indole-2-carboxylic acid (206.3 mg, 1.08 mmol, 1 eq) and HOBt (153.1 mg, 1.1 mmol, 1.0 eq) in DCM (6 mL) was added EDCI (223.5 mg, 1.17 mmol, 1.0 eq) and tert-butyl (2S)-2-amino-3-cyclopropyl-propanoate (200 mg, 1.08 mmol, 1 eq). The mixture was stirred at 25 °C for 16 h. TLC (petroleum ether: ethyl acetate=2/1, UV). The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/rthyl acetate=100/1 to 2/1) to give *tert*-butyl (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoate (150 mg, 38% yield) as a yellow solid.

Step 7: (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid

[0001307] To a solution of *tert*-butyl (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoate (100 mg, 0.27 mmol, 1 eq) in DCM (1 mL) was added TFA (7.7 g, 67.5 mmol, 5.0 mL, 242.05 eq) and the resulting mixture was stirred at 25 °C for 1 h. TLC (petroleum ether: ethyl acetate=2/1, UV). The reaction mixture was concentrated

under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=100/1 to 2/1) to give (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (50 mg, 59.2% yield) as a white solid.

Step 8: N-[(1S)-2-[[2-amino-2-oxo-1-[(2-oxoimidazolidin-1-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[0001308] To a solution of (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (50 mg, 0.16 mmol, 1 eq) in DMF (2 mL) was added HATU (94.3 mg, 0.24 mmol, 1.5 eq), 2-amino-3-(2-oxoimidazolidin-1-yl)propanamide (42.7 mg, 0.24 mmol, 1.5 eq) and DIPEA (53.4 mg, 0.41 mmol, 72.0 uL, 2.5 eq). The mixture was stirred at 25 °C for 1 h. TLC (dichloromethane: methanol=10/1, UV). The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=100/1 to 10/1) to give 10 (60 mg, 79% yield) as a white solid.

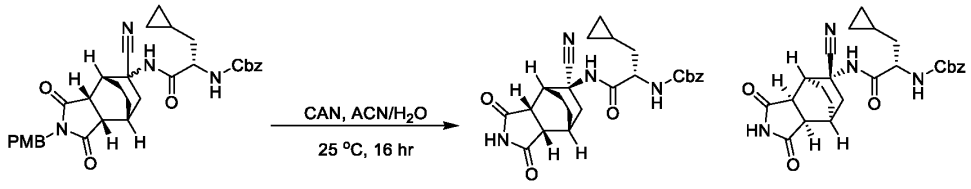
Step 9: N-[(1S)-2-[[1-cyano-2-(2-oxoimidazolidin-1-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[0001309] To a solution of 10 (60 mg, 0.13 mmol, 1 eq) in DCM (3.0 mL) was added Burgess reagent (93.9 mg, 0.39 mmol, 3.0 eq). The mixture was stirred at 25 °C for 16 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 21%-51%, 9.5 min) to give N-[(1S)-2-[[1-cyano-2-(2-oxoimidazolidin-1-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (9.72 mg, 16% yield) as a white solid.

[0001310] LCMS: Rt = 0.772 min; for $C_{22}H_{26}N_6O_4$ MS Calcd.: 438.20; MS Found: 439.1 [$M+H^+$].

[0001311] ^1H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1H), 7.19 - 7.12 (m, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.52 (d, J = 7.6 Hz, 1H), 5.22 - 5.01 (m, 1H), 4.59 (s, 1H), 3.93 (s, 3H), 3.62 - 3.52 (m, 4H), 3.44 - 3.34 (m, 2H), 1.92 - 1.78 (m, 1H), 1.70 (tt, J = 6.8, 13.2 Hz, 1H), 0.83 (d, J = 6.0 Hz, 1H), 0.61 - 0.40 (m, 2H), 0.27 - 0.08 (m, 2H).

Example 157. Synthesis of viral protease inhibitor compound 495



[0001312] Isomer 1: benzyl *N*-[(1*S*)-2-[[(1*R*,2*S*,6*R*,7*R*,8*S*)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate; Isomer 2: Benzyl *N*-[(1S)-2-[[(1*S*,2*R*,6*S*,7*S*,8*R*)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate

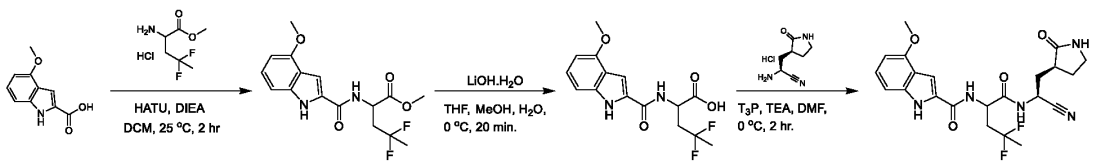
[0001313] A mixture of benzyl *N*-[(1*S*)-2-[[(1*R*,2*S*,6*R*,7*R*)-8-cyano-4-[(4-methoxyphenyl)methyl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (200 mg, 0.34 mmol, 1 *eq*), ammonia; cerium(4+); nitric acid; tetranitrate (1.13 g, 2.05 mmol, 1.02 mL, 6 *eq*) in H_2O (1 mL) and MeCN (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 16 h under N_2 atmosphere. The mixture was quenched with H_2O (20 mL), and extracted with ethyl acetate (40 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by *prep*-HPLC (column: 3_Phenomenex Luna C18 75 * 30 mm * 3 um; mobile phase: [water(0.05% HCl)-ACN]; B%: 25%-55%, 8.5 min) to give benzyl *N*-[(1*S*)-2-[[(1*R*,2*S*,6*R*,7*R*,8*S*)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (17.25 mg, 35.6 umol, 10.4% yield, 96.1% purity) was obtained as a white solid and benzyl *N*-[(1*S*)-2-[[(1*S*,2*R*,6*S*,7*S*,8*R*)-8-cyano-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undecan-8-yl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (17.56 mg, 36.37 umol, 10.63% yield, 96.2% purity) was obtained as a white solid.

[0001314] Isomer 1: LCMS: Rt = 0.798 min; for $C_{25}H_{28}N_4O_5$ MS Calcd.: 464.21; MS Found: 465.1 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 - 7.21 (m, 5H), 5.17 - 5.08 (m, 2H), 4.10 (dd, *J*=4.3, 9.8 Hz, 1H), 3.12 (br d, *J*=2.5 Hz, 1H), 3.01 - 2.88 (m, 2H), 2.42 - 2.28 (m, 2H), 2.20 - 2.09 (m, 1H), 1.89 (br d, *J*=15.3 Hz, 1H), 1.80 - 1.73 (m, 2H),

1.72 - 1.61 (m, 2H), 1.56 (br d, *J*=7.5 Hz, 1H), 0.82 - 0.67 (m, 1H), 0.42 - 0.42 (m, 1H), 0.48 - 0.38 (m, 1H), 0.23 - 0.09 (m, 2H).

[0001315] Isomer 2: LCMS: Rt = 0.818 min; for $C_{25}H_{28}N_4O_5$ MS Calcd.: 464.21; MS Found: 465.1 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 - 7.25 (m, 5H), 5.18 - 5.09 (m, 2H), 4.17 (br dd, *J*=6.0, 7.6 Hz, 1H), 3.35 (s, 1H), 3.11 - 2.93 (m, 2H), 2.42 (br d, *J*=15.6 Hz, 1H), 2.31 (br s, 1H), 2.23 - 2.12 (m, 1H), 1.91 (br d, *J*=15.3 Hz, 1H), 1.76 (br d, *J*=6.8 Hz, 2H), 1.68 (br d, *J*=11.4 Hz, 1H), 1.65 - 1.58 (m, 1H), 1.56 - 1.45 (m, 1H), 0.78 - 0.67 (m, 1H), 0.44 (d, *J*=5.1 Hz, 2H), 0.12 (br s, 2H).

Example 158. Synthesis of viral protease inhibitor compound 496



Step 1: Methyl 4,4-difluoro-2-[(4-methoxy-1H-indole-2-carbonyl)amino]pentanoate

[0001316] To a solution of 4-methoxy-1*H*-indole-2-carboxylic acid (281.6 mg, 1.47 mmol, 1 *eq*) in DCM (1 mL) was added HATU (672.2 mg, 1.77 mmol, 1.2 *eq*), DIPEA (571.2 mg, 4.42 mmol, 0.76 mL, 3 *eq*) and methyl 2-amino-4,4-difluoro-pentanoate (300 mg, 1.47 mmol, 1 *eq*, HCl). The mixture was stirred at 25 °C for 2 h. TLC (petroleum ether: ethyl acetate = 0:1). The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% petroleum ether/ethyl acetate ethergradient @ 20 mL/min) to give methyl 4,4-difluoro-2-[(4-methoxy-1*H*-indole-2-carbonyl)amino]pentanoate (357 mg, 1.04 mmol, 70.7% yield, 99.4% purity) as a yellow solid.

Step 2: 4,4-Difluoro-2-[(4-methoxy-1H-indole-2-carbonyl)amino]pentanoic acid

[0001317] To a solution of methyl 4,4-difluoro-2-[(4-methoxy-1*H*-indole-2-carbonyl)amino]pentanoate (357 mg, 1.05 mmol, 1 *eq*) in THF (3 mL) and MeOH (1 mL) was added LiOH.H_2O (132.0 mg, 3.15 mmol, 3 *eq*) in H_2O (2 mL) at 0 °C, The mixture was stirred at 0 °C for 20 min. The pH of the reaction was adjusted to about 4 with 4 M

HCl. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic phase was washed with brine (5 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was used into the next step without further purification. Compound 4,4-difluoro-2-[(4-methoxy-1*H*-indole-2-carbonyl)amino]pentanoic acid (321 mg, 93.7% yield) was obtained as a light yellow solid.

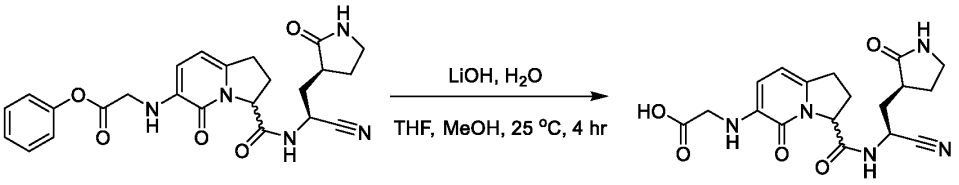
Step 3: N-[1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3,3-difluoro-butyl]-4-methoxy-1H-indole-2-carboxamide

[0001318] To a solution of 4,4-difluoro-2-[(4-methoxy-1*H*-indole-2-carbonyl)amino]pentanoic acid (20 mg, 61.2 umol, 1 *eq*) in DCM (0.5 mL) was added (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanenitrile (13.9 mg, 73.5 umol, 1.2 *eq*, HCl), TEA (18.6 mg, 0.18 mmol, 25.5 uL, 3 *eq*) and T_3P (50.7 mg, 79.6 umol, 50% purity, 1.3 *eq*) in DMF (0.2 mL). The mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 17%-47%,9.5 min) to give *N*-[1-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3,3-difluoro-butyl]-4-methoxy-1*H*-indole-2-carboxamide (2.54 mg, 8.7% yield, 97.7% purity) as a white solid.

[0001319] LCMS: Rt = 0.772 min; for $C_{22}H_{25}F_2N_5O_4$ MS Calcd.: 461.19; MS Found: 462.1 [$M+H^+$].

[0001320] ^1H NMR (400 MHz, CD_3OD) δ 7.24 (d, *J* = 3.8 Hz, 1H), 7.15 (dt, *J* = 2.3, 8.0 Hz, 1H), 7.03 (dd, *J* = 2.5, 8.3 Hz, 1H), 6.52 (dd, *J* = 1.5, 7.5 Hz, 1H), 5.07 - 5.00 (m, 1H), 4.84 (br s, 1H), 3.93 (d, *J* = 1.8 Hz, 3H), 3.30 - 3.18 (m, 2H), 2.67 - 2.57 (m, 1H), 2.56 - 2.40 (m, 2H), 2.37 - 2.25 (m, 2H), 1.95 - 1.85 (m, 1H), 1.85 - 1.76 (m, 1H), 1.69 (dt, *J* = 2.6, 18.8 Hz, 3H).

Example 159. Synthesis of viral protease inhibitor compound 501

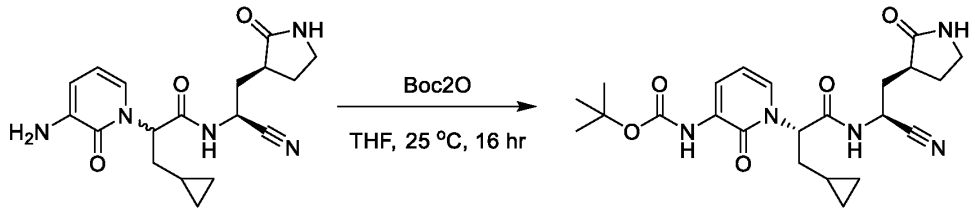


[0001321] To a solution of phenyl 2-[[(3*S*)-3-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-5-oxo-2,3-dihydro-1H-indolizin-6-yl]amino]acetate (100 mg, 0.21 mmol, 1 ***eq***) in THF (1 mL) and MeOH (0.3 mL) was added $LiOH.H_2O$ (27.1 mg, 0.64 mmol, 3 *eq*) in H_2O (0.5 mL). The mixture was stirred at 25 °C for 4 h. LC-MS and HPLC showed the desired compound was detected. The pH of the reaction was adjusted to about 1 with 4 M HCl. The reaction mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL * 3). The combined organic phase was washed with brine (5 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75*30 mm*3 um; mobile phase: [water (0.05% HCl)-ACN]; B%: 0%-30%, 8.5 min). The residue was checked by LCMS and HPLC. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75*30 mm*3 um; mobile phase: [water (0.05% HCl)-ACN]; B%: 0%-30%, 8.5 min). Compound 2-[[(3*S*)-3-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-5-oxo-2,3-dihydro-1H-indolizin-6-yl]amino]acetic acid (1.2 mg, 1.27% yield, 98.9% purity, CHOOH) was obtained as a white solid.

[0001322] LCMS: Rt = 0.643 min; for $C_{18}H_{21}N_5O_5$ MS Calcd.: 387.15; MS Found: 388.1 [$M+H^+$].

[0001323] ^1H NMR (400 MHz, CD_3OD) δ 8.49 (br s, 1H), 8.03 (s, 1H), 6.32 (d, *J* = 7.5 Hz, 1H), 5.09 - 5.03 (m, 2H), 3.74 (s, 2H), 3.34 (br s, 1H), 3.26 - 3.18 (m, 2H), 3.17 - 3.07 (m, 1H), 2.74 - 2.64 (m, 1H), 2.62 - 2.51 (m, 1H), 2.40 - 2.26 (m, 3H), 2.24 - 2.15 (m, 1H), 1.97 - 1.88 (m, 1H), 1.87 - 1.77 (m, 1H).

Example 160. Synthesis of viral protease inhibitor compound 505

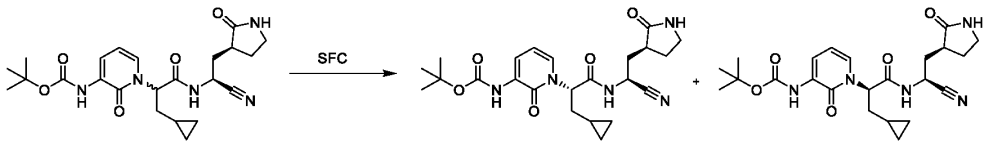


[0001324] To a solution of 2-(3-amino-2-oxo-1-pyridyl)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (100 mg, 0.27 mmol, 1 *eq*) in THF (1 mL) was added Boc2O (610.6 mg, 2.80 mmol, 0.64 mL, 10 *eq*). The mixture was stirred at 25 °C for 16 h. TLC (DCM: MeOH = 10:1). The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by *prep*-TLC (SiO_2, DCM: MeOH = 20:1) to give *tert*-butyl N-[1-[2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-2-oxo-3-pyridyl]carbamate (12.62 mg, 9.0 % yield, 91.4 % purity) as a white solid.

[0001325] LCMS: Rt = 0.832 min; for $C_{23}H_{31}N_5O_5$ MS Calcd.: 457.23; MS Found: 458.2 [$M+H^+$].

[0001326] ^1H NMR (400 MHz, CD_3OD) δ 7.98 (d, *J* = 6.3 Hz, 1H), 7.39 - 7.31 (m, 1H), 6.45 - 6.34 (m, 1H), 5.56 - 5.39 (m, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 3.34 (s, 1H), 3.29 - 3.22 (m, 1H), 2.57 - 2.43 (m, 1H), 2.41 - 2.30 (m, 1H), 2.29 - 2.20 (m, 1H), 2.01 - 1.94 (m, 2H), 1.92 - 1.72 (m, 2H), 1.52 (d, *J* = 2.5 Hz, 9H), 0.62 (dd, *J* = 7.4, 12.3 Hz, 1H), 0.50 - 0.36 (m, 2H), 0.21 - 0.12 (m, 1H), 0.09 - 0.02 (m, 1H).

Example 161. Synthesis of viral protease inhibitor compound 504

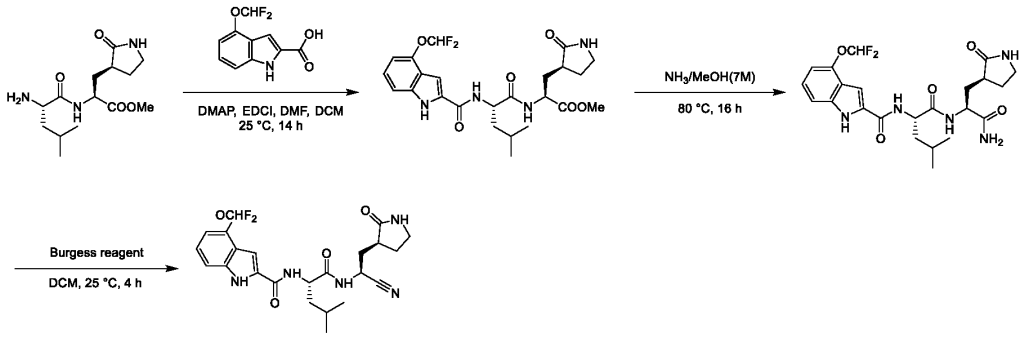


[0001327] The residue was further separated by SFC. The residue was further separated by SFC (column: DAICEL CHIRALPAK AS (250 mm*30 mm, 10 um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 30%-30%, min).

[0001328] Isomer 1: Compound *tert*-butyl *N*-[1-[(1*R*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-2-oxo-3-pyridyl]carbamate (2.47 mg, 23.1% yield) was obtained as a white solid. LCMS: Rt = 0.837 min; for $C_{23}H_{31}N_5O_5$ MS Calcd.: 457.23; MS Found: 458.1 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, *J* = 7.1 Hz, 1H), 7.34 (dd, *J* = 1.7, 7.1 Hz, 1H), 6.39 (t, *J* = 7.2 Hz, 1H), 5.56 - 5.31 (m, 1H), 5.01 (dd, *J* = 6.8, 9.3 Hz, 1H), 3.34 (d, *J* = 2.8 Hz, 2H), 2.56 - 2.44 (m, 1H), 2.41 - 2.32 (m, 1H), 2.32 - 2.24 (m, 1H), 2.00 - 1.91 (m, 3H), 1.89 - 1.82 (m, 1H), 1.52 (s, 9H), 0.59 (s, 1H), 0.46 - 0.37 (m, 2H), 0.15 (d, *J* = 8.4 Hz, 1H), 0.03 (d, *J* = 11.3 Hz, 1H).

[0001329] Isomer 2: Compound *tert*-butyl *N*-[1-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-2-oxo-3-pyridyl]carbamate (2.71 mg, 25.5% yield) was obtained as a white solid. LCMS: Rt = 0.837 min; for $C_{23}H_{31}N_5O_5$ MS Calcd.: 457.23; MS Found: 458.1 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, *J* = 7.3 Hz, 1H), 7.35 (dd, *J* = 1.8, 7.0 Hz, 1H), 6.38 (t, *J* = 7.3 Hz, 1H), 5.42 (dd, *J* = 7.0, 8.5 Hz, 1H), 5.44 - 5.40 (m, 1H), 5.03 - 4.99 (m, 1H), 3.30 - 3.25 (m, 2H), 2.48 (dq, *J* = 5.3, 9.2 Hz, 1H), 2.29 - 2.22 (m, 1H), 2.32 - 2.22 (m, 1H), 2.02 - 1.94 (m, 2H), 1.91 - 1.85 (m, 1H), 1.84 - 1.73 (m, 1H), 1.51 (s, 9H), 0.63 (br d, *J* = 6.8 Hz, 1H), 0.49 - 0.42 (m, 2H), 0.18 - 0.13 (m, 1H), 0.06 (dd, *J* = 4.3, 8.8 Hz, 1H).

Example 162. Synthesis of viral protease inhibitor compound 509



Step 1: methyl (2S)-2-[[(2S)-2-[[4-(difluoromethoxy)-1H-indole-2-carbonyl]amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001330] To a mixture of methyl (2S)-2-[[(2S)-2-amino-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (160 mg, 476.44 umol, 1 *eq*, HCl) and 4-

(difluoromethoxy)-1H-indole-2-carboxylic acid (108.23 mg, 476.44 umol, 1 *eq*) in DCM (4 mL) was added DMAP (174.62 mg, 1.43 mmol, 3 *eq*) and EDCI (274.00 mg, 1.43 mmol, 3 *eq*), The mixture was added DMF (1 mL) and stirred at 25 °C for 14 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-60%,10 min). Compound methyl (2S)-2-[[(2S)-2-[[4-(difluoromethoxy)-1H-indole-2-carbonyl]amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 294.98 umol, 61.91% yield) was obtained as a white solid. MS (ESI) *m/z* 494.3 $[M+H]^+$

Step 2: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-(difluoromethoxy)-1H-indole-2-carboxamide

[0001331] A mixture of methyl (2S)-2-[[(2S)-2-[[4-(difluoromethoxy)-1H-indole-2-carbonyl]amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 294.98 umol, 1 *eq*) in ammonia (7.65 g, 449.19 mmol, 7.50 mL, 1522.81 *eq*) was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-(difluoromethoxy)-1H-indole-2-carboxamide (100 mg, 202.63 umol, 68.69% yield) was obtained as a white solid and used for the next step. MS (ESI) *m/z* 494.3 $[M+H]^+$

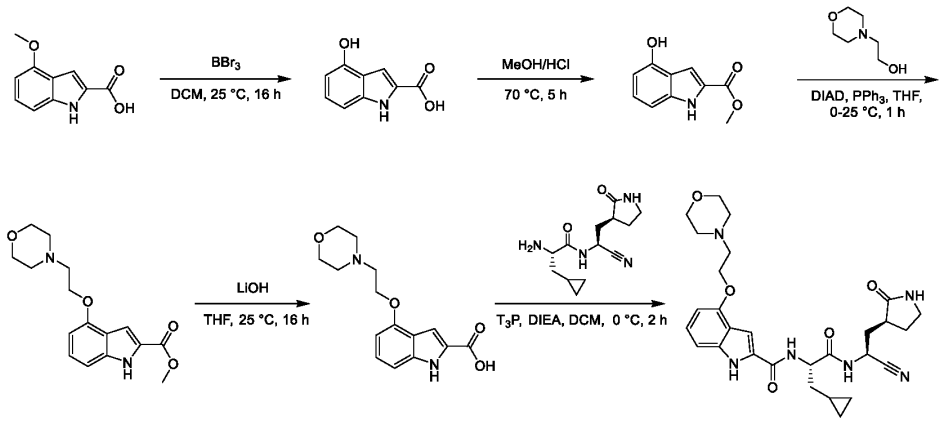
Step 3: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-(difluoromethoxy)-1H-indole-2-carboxamide

[0001332] To a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3-methyl-butyl]-4-(difluoromethoxy)-1H-indole-2-carboxamide (100 mg, 202.63 umol, 1 *eq*) in DCM (3 mL) was added Burgess reagent (193.16 mg, 810.53 umol, 4 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-60%, 10 min). Compound N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl-butyl]-4-(difluoromethoxy)-1H-indole-2-carboxamide (30

mg, 63.09 umol, 31.14% yield) was obtained as a white solid. MS (ESI) *m/z* 476.3 $[M+H]^+$

[0001333] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.88 (d, *J*=1.8 Hz, 1H), 8.93 (d, *J*=8.1 Hz, 1H), 8.65 (d, *J*=7.7 Hz, 1H), 7.78 - 7.67 (m, 1H), 7.43 (d, *J*=1.5 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.21 - 7.12 (m, 1H), 6.82 (d, *J*=7.6 Hz, 1H), 5.04 - 4.85 (m, 1H), 4.56 - 4.40 (m, 1H), 3.20 - 3.03 (m, 2H), 2.42 - 2.04 (m, 3H), 1.85 - 1.47 (m, 5H), 1.00 - 0.84 (m, 6H)

Example 163. Synthesis of viral protease inhibitor compound 515



Step 1: 4-hydroxy-1H-indole-2-carboxylic acid

[0001334] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (500 mg, 2.62 mmol, 1 *eq*) in DCM (10 mL) was added BBr_3 (1.31 g, 5.23 mmol, 2 eq) at 0 °C. The mixture was stirred at 25 °C for 16 h. The mixture was diluted with H_2O (30 mL) and extracted with DCM (60 mL, which was extracted as 30 mL * 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-hydroxy-1H-indole-2-carboxylic acid (200 mg, crude) as a red solid. MS (ESI) m/z 176.1 [M-H]+

Step 2: methyl 4-hydroxy-1H-indole-2-carboxylate

[0001335] 4-hydroxy-1H-indole-2-carboxylic acid (200 mg, 1.13 mmol, 1 *eq*) was added HCl/MeOH (4 M, 10 mL, 35.43 *eq*). The mixture was stirred at 70 °C for 5 h. The reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=9/1

to 8/1) to give methyl 4-hydroxy-1H-indole-2-carboxylate (170 mg, 800.28 umol, 70.89% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 190.1 $[M-H]^+$

Step 3: methyl 4-(2-morpholinoethoxy)-1H-indole-2-carboxylate

[0001336] To a mixture of methyl 4-hydroxy-1H-indole-2-carboxylate (300 mg, 1.57 mmol, 1 *eq*) and 2-morpholinoethanol (205.83 mg, 1.57 mmol, 192.37 uL, 1 *eq*) in THF (4 mL) was added PPh_3 (452.73 mg, 1.73 mmol, 1.1 *eq*), DIAD (317.30 mg, 1.57 mmol, 305.10 uL, 1 *eq*) was added at 0 °C under N_2. The mixture was stirred at 25 °C for 60 min. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 2). The combined organic layers were washed with brine 20 mL, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC(petroleum ether:ethyl acetate=0:1) to give methyl 4-(2-morpholinoethoxy)-1H-indole-2-carboxylate (200 mg, 591.44 umol, 37.69% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 304.9 $[M+H]^+$

Step 4: 4-(2-morpholinoethoxy)-1H-indole-2-carboxylic acid

[0001337] To a mixture of methyl 4-(2-morpholinoethoxy)-1H-indole-2-carboxylate (200 mg, 657.16 umol, 1 *eq*) in THF (2 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (41.37 mg, 985.74 umol, 1.5 *eq*) at 25 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude was purified by HCl prep-HPLC to give 4-(2-morpholinoethoxy)-1H-indole-2-carboxylic acid (80 mg, 261.79 umol, 39.84% yield, 95% purity) as a white solid. MS (ESI) *m/z* 289.2 $[M-H]^+$

[0001338] column: Phenomenex luna C18 80*40 mm*3 um; mobile phase: [water(0.04% HCl)-ACN];B%: 1%-32%,6.5 min

Step 5: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-(2-morpholinoethoxy)-1H-indole-2-carboxamide

[0001339] To a mixture of 4-(2-morpholinoethoxy)-1H-indole-2-carboxylic acid (70 mg, 241.12 umol, 1 *eq*) and (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (159.33 mg, 241.12 umol, 40% purity, 1 *eq*) in DCM (2 mL) was added DIEA (93.49 mg, 723.36 umol, 125.99 uL, 3 *eq*) and T_3P (230.16 mg, 361.68 umol, 215.10 uL, 50% purity, 1.5 *eq*) in one portion at 0 °C. The

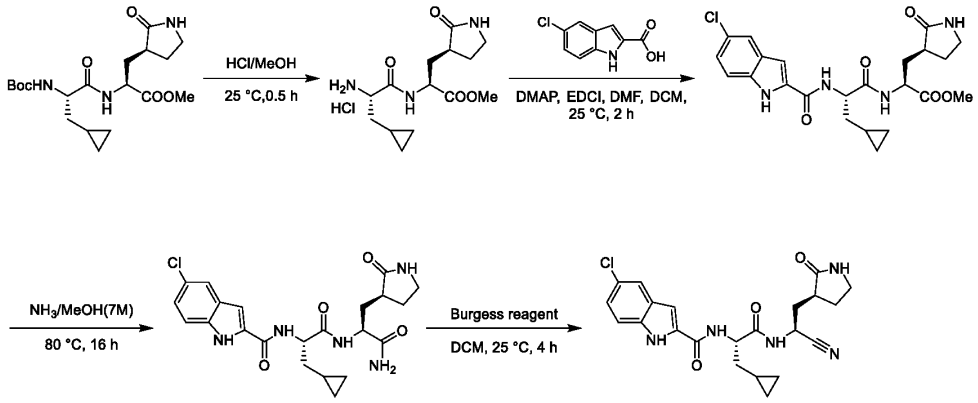
mixture was stirred at 0 °C for 2 h. The reaction mixture was added EDTA solution (2 mL) and stirred at 25 °C for 10 min, and then extracted with DCM (6 mL, which was extracted as 2 mL * 3). The combined organic layers were washed with brine (5 mL, which was washed as 5 mL * 3), and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-(2-morpholinoethoxy)-1H-indole-2-carboxamide (13 mg, 24.23 umol, 10.05% yield) as a white solid. MS (ESI) *m/z* 537.3 $[M+H]^+$

column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 20%-50%,8 min

[0001340] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.57 (s, 1H), 8.92 (d, *J*=7.9 Hz, 1H), 8.60 (br d, *J*=7.5 Hz, 1H), 7.79 - 7.68 (m, 1H), 7.35 (d, *J*=1.5 Hz, 1H), 7.14 - 6.93 (m, 2H), 6.51 (d, *J*=7.5 Hz, 1H), 4.98 (q, *J*=7.9 Hz, 1H), 4.54 - 4.38 (m, 1H), 4.21 (br d, *J*=3.5 Hz, 2H), 3.59 (t, *J*=4.5 Hz, 4H), 3.20 - 3.05 (m, 2H), 2.78 (t, *J*=5.6 Hz, 2H), 2.60 - 2.52 (m, 4H), 2.43 - 2.28 (m, 1H), 2.23 - 2.04 (m, 2H), 1.92 - 1.60 (m, 3H), 1.56 - 1.38 (m, 1H), 0.80 (br d, *J*=5.3 Hz, 1H), 0.51 - 0.30 (m, 2H), 0.25 - 0.05 (m, 2H)

[0001341] ^{1}H NMR (400MHz, METHANOL-d_4) δ = 7.34 - 7.28 (m, 1H), 7.18 - 7.11 (m, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 6.53 (d, *J*=7.5 Hz, 1H), 5.08 (dd, *J*=5.8, 10.3 Hz, 1H), 4.54 (t, *J*=7.4 Hz, 1H), 4.30 (t, *J*=5.3 Hz, 2H), 3.77 - 3.72 (m, 4H), 3.30 - 3.27 (m, 2H), 2.92 (t, *J*=5.3 Hz, 2H), 2.75 - 2.59 (m, 5H), 2.40 - 2.26 (m, 2H), 1.99 - 1.79 (m, 3H), 1.78 - 1.60 (m, 1H), 0.93 - 0.76 (m, 1H), 0.58 - 0.52 (m, 2H), 0.20 (br dd, *J*=5.0, 11.6 Hz, 2H)

Example 164. Synthesis of viral protease inhibitor compound 519



Step 1: methyl(2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl] propanoate

[0001342] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (230 mg, 578.67 umol, 1 *eq*) in HCl/MeOH (3 mL) was stirred at 25 °C for 30 min. The reaction mixture was concentrated under reduced pressure to give the crude methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (170 mg, 571.72 umol, 98.80% yield) as a white solid.

Step 2: methyl(2S)-2-[[(2S)-2-[(5-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001343] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (170 mg, 571.72 umol, 1 *eq*) in DCM (2 mL) and DMF (0.5 mL) was added DMAP (209.54 mg, 1.72 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added with 5-chloro-1H-indole-2-carboxylic acid (134.20 mg, 686.06 umol, 1.2 *eq*) and EDCI (328.80 mg, 1.72 mmol, 3 *eq*) and stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-TLC (SiO_2, EA: MeOH = 10:1) to give methyl(2S)-2-[[(2S)-2-[(5-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (140 mg, 294.78 umol, 51.56% yield) as a white solid. MS (ESI) *m/z* 475.2 $[M+H]^+$

Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1- (cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1H-indole-2-carboxamide

[0001344] To a mixture of methyl (2S)-2-[[(2S)-2-[(5-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (130 mg, 273.72 umol, 1 *eq*) in NH_3/MeOH(7M) (5 mL), the mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1- (cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1H-indole-2-carboxamide (100 mg, 217.43 umol, 79.43% yield) as a white solid. MS (ESI) *m/z* 460.2 $[M+H]^+$

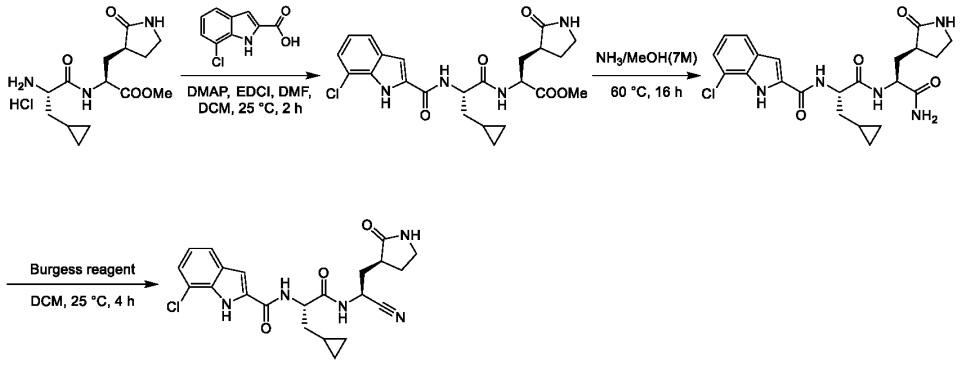
Step 4: 5-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropyl methyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001345] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1H-indole-2-carboxamide (100 mg, 217.43 umol, 1 *eq*) in DCM (2 mL) was added Burgess reagent (103.63 mg, 434.85 umol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give 5-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (33 mg, 74.68 umol, 34.35% yield) as a white solid. MS (ESI) *m/z* 442.1 $[M+H]^+$

[0001346] Column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-60%,8 min

[0001347] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.71 (s, 1H), 8.85 (d, *J*=8.2 Hz, 1H), 8.59 (d, *J*=7.5 Hz, 1H), 7.71 - 7.56 (m, 2H), 7.34 (d, *J*=8.6 Hz, 1H), 7.19 (s, 1H), 7.10 (dd, *J*=1.5, 8.8 Hz, 1H), 4.97 - 4.80 (m, 1H), 4.48 - 4.30 (m, 1H), 3.12 - 2.94 (m, 2H), 2.36 - 2.21 (m, 1H), 2.13 - 1.96 (m, 2H), 1.83 - 1.54 (m, 3H), 1.47 - 1.34 (m, 1H), 0.82 - 0.65 (m, 1H), 0.39 - 0.26 (m, 2H), 0.19 - 0.04 (m, 2H)

Example 165. Synthesis of viral protease inhibitor compound 531



Step 1: methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001348] A mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.68 mmol, 1 *eq*) in DCM (10 mL) and DMF (2.5 mL), the mixture was added DMAP (616.30 mg, 5.04 mmol, 3 *eq*) in one portion at 25 °C. The mixture was added with 7-chloro-1H-indole-2-carboxylic acid (394.69 mg, 2.02 mmol, 1.2 *eq*) and EDCI (967.04 mg, 5.04 mmol, 3 *eq*) and the reaction was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 5/1 to 0/1) to give methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (550 mg, 1.16 mmol, 68.87% yield) as a white solid. MS (ESI) *m/z* 475.1 $[M+H]^+$

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide

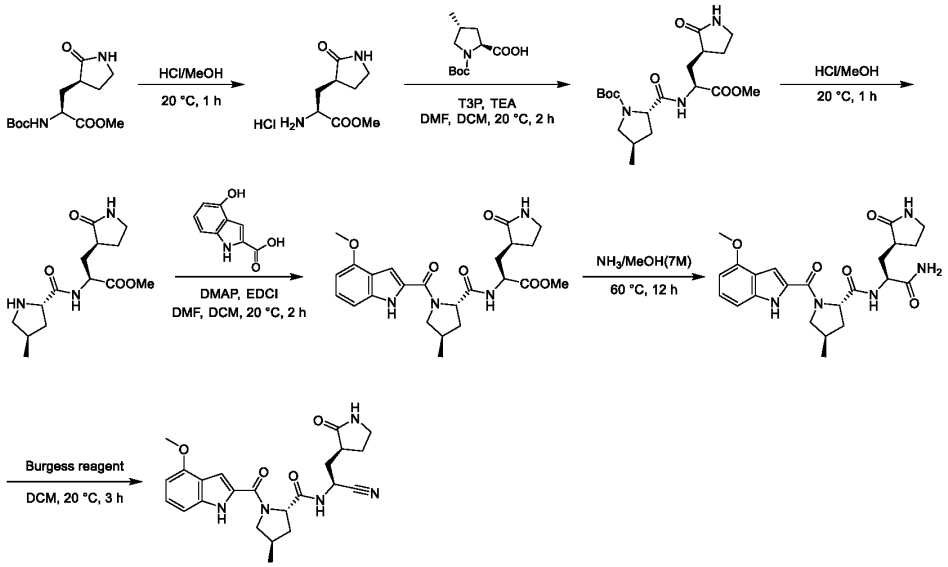
[0001349] A mixture of methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.05 mmol, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 66.49 *eq*) was stirred at 60 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (440 mg, 956.68 umol, 90.87% yield) as a white solid. MS (ESI) *m/z* 460.3 $[M+H]^+$

Step 3: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001350] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (430 mg, 934.94 umol, 1 *eq*) in DCM (6 mL) was added Burgess reagent (445.61 mg, 1.87 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+ 10 mM NH_4HCO_3)-ACN];B%: 30%-60%,8 min) to give 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (180 mg, 407.32 umol, 43.57% yield) as a white solid. MS (ESI) *m/z* 442.2 $[M+H]^+$

[0001351] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.71 (br s, 1H), 9.01 (d, *J*=7.9 Hz, 1H), 8.72 (d, *J*=7.5 Hz, 1H), 7.71 (s, 1H), 7.63 (dd, *J*=0.7, 7.9 Hz, 1H), 7.34 - 7.25 (m, 2H), 7.07 (t, *J*=7.8 Hz, 1H), 5.00 (q, *J*=7.9 Hz, 1H), 4.58 - 4.49 (m, 1H), 3.13 (quin, *J*=9.2 Hz, 2H), 2.42 - 2.31 (m, 1H), 2.22 - 2.05 (m, 2H), 1.89 - 1.64 (m, 3H), 1.57 - 1.46 (m, 1H), 0.89 - 0.75 (m, 1H), 0.50 - 0.37 (m, 2H), 0.25 - 0.07 (m, 2H)

Example 166. Synthesis of viral protease inhibitor compound 539



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[0001352] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.75 mmol, 1 eq) in HCl/MeOH (4 M, 20 mL, 45.81 eq) was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to get the product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (350 mg, crude, HCl) as a yellow solid.

Step 2: (2S,4R)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-4-methylpyrrolidine-1-carboxylate

[0001353] To a solution of (2S,4R)-1-tert-butoxycarbonyl-4-methyl-pyrrolidine-2-carboxylic acid (250 mg, 1.09 mmol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (304.45 mg, 1.64 mmol, 1.5 eq) in DCM (10 mL) was added drop-wise T3P (1.04 g, 1.64 mmol, 972.75 uL, 50% purity, 1.5 eq) and Et_3N (662.02 mg, 6.54 mmol, 910.62 uL, 6 eq), and the reaction was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition H_2O (40 mL) at 0 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine 40 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 10:1 to 0:1) to get the product tert-butyl (2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-methyl-pyrrolidine-1-carboxylate (320 mg, 805.10 umol, 73.86% yield) as a colorless oil. MS (ESI) *m/z* 398.2 $[M+H]^+$.

Step 3: (S)-methyl 2-((2S,4R)-4-methylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001354] A solution of tert-butyl (2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-methyl-pyrrolidine-1-carboxylate (260 mg, 654.15 umol, 1 eq) in HCl/MeOH (4 M, 8 mL, 48.92 eq) was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to get the product methyl (2S)-2-[[(2S,4R)-4-methylpyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, crude, HCl) as a colorless oil. MS (ESI) *m/z* 298.2 $[M+H]^+$.

Step 4: (S)-methyl 2-((2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4-methylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001355] To a solution of methyl (2S)-2-[[(2S,4R)-4-methylpyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 599.14 umol, 1 eq,

HCl) and 4-methoxy-1H-indole-2-carboxylic acid (229.09 mg, 1.20 mmol, 2.0 eq) in DMF (2.0 mL) was added DMAP (219.59 mg, 1.80 mmol, 3.0 eq) and EDCI (229.71 mg, 1.20 mmol, 2 eq) and DCM (8.0 mL), the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition H_2O (50 mL) at 0 °C, and then extracted with DCM (40 mL * 3). The combined organic layers were washed with brine 60 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 1:1 to 0:1) to get the product methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 494.14 umol, 82.47% yield, 93% purity) as a yellow solid. MS (ESI) *m/z* 471.3 $[M+H]^+$.

*Step 5: (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamid*e

[0001356] A solution of methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (220 mg, 434.84 umol, 93% purity, 1 eq) in NH_3/MeOH (7 M, 20 mL, 321.96 eq)was stirred at 60 °C for 12 h. The reaction mixture was concentrated under reduced pressure to get the product (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide (200 mg, crude) as a yellow solid. MS (ESI) *m/z* 456.2 $[M+H]^+$.

Step 6: (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide

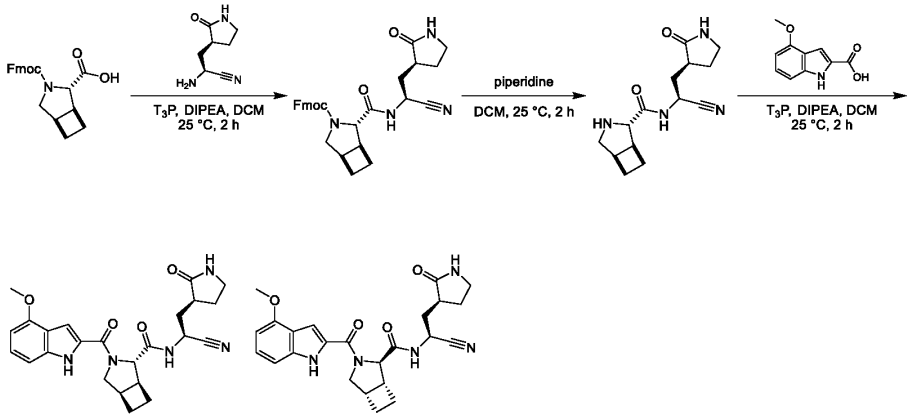
[0001357] To a solution of (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide (100 mg, 219.54 umol, 1 eq) in DCM (5 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (313.90 mg, 1.32 mmol, 6 eq), and the mixture was stirred at 20 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 um; mobile phase: [water (0.2% FA) - ACN]; B%: 25% - 60%, 8 min) to get the product (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-

methoxy-1H-indole-2-carbonyl)-4-methyl-pyrrolidine-2-carboxamide (33 mg, 75.43 umol, 34.36% yield, 100% purity) as a white solid. MS (ESI) *m/z* 438.2 $[M+H]^+$.

[0001358] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.73 - 11.47 (m, 1H), 8.85 (br d, J = 8.3 Hz, 1H), 7.84 - 7.54 (m, 1H), 7.24 - 6.84 (m, 3H), 6.74 - 6.48 (m, 1H), 5.10 - 4.47 (m, 2H), 4.20- 3.75 (m, 4H), 3.47 (t, J = 9.0 Hz, 1H), 3.16 (d, J = 7.9 Hz, 1H), 2.61 (s, 1H), 2.43 - 2.36 (m, 1H), 2.27 - 1.43 (m, 7H), 1.07 (d, J = 6.4 Hz, 3H).

[0001359] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.25 - 6.75 (m, 3H), 6.59 - 6.40 (m, 1H), 5.15 - 5.00 (m, 1H), 4.84 - 4.61 (m, 1H), 4.30 - 4.06 (m, 1H), 3.98 - 3.84 (m, 3H), 3.55 (t, J = 8.9 Hz, 1H), 3.30 - 3.24 (m, 1H), 3.01 - 2.54 (m, 2H), 2.46 - 2.09 (m, 4H), 2.01 - 1.38 (m, 3H), 1.15 (br d, J = 6.6 Hz, 3H).

Example 167. Synthesis of viral protease inhibitor compound 547



Step 1: 9H-fluoren-9-ylmethyl (1S,2S,5R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-azabicyclo[3.2.0]heptane-3-carboxylate

[0001360] (1S,2S,5R)-3-(9H-fluoren-9-ylmethoxycarbonyl)-3-azabicyclo[3.2.0]heptane-2-carboxylic acid (250 mg, 687.94 umol, 1 eq), (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanenitrile (486.36 mg, 825.52 umol, 26% purity, 1.2 eq) in DCM (3 mL) was added T_3P (656.67 mg, 1.03 mmol, 613.71 uL, 50% purity, 1.5 eq) and DIEA (266.73 mg, 2.06 mmol, 359.48 uL, 3 eq), the solution was stirred at 25 °C for 2 h. After completion, the solution was diluted with H_2O (20 mL), extracted with ethyl acetate (30 mL * 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1).

9H-fluoren-9-ylmethyl (1S,2S,5R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-azabicyclo[3.2.0]heptane-3-carboxylate (185 mg, 371.06 umol, 53.94% yield, 100% purity) was obtained as yellow solid. MS (ESI) *m/z* 499.2 $[M+H]^+$.

Step 2: (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-azabicyclo[3.2.0]heptane-2-carboxamide

[0001361] To a solution of 9H-fluoren-9-ylmethyl (1S,2S,5R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-azabicyclo[3.2.0]heptane-3-carboxylate (440 mg, 706.02 umol, 80% purity, 1 eq) in DCM (4.5 mL) was added the piperidine (60.11 mg, 706.02 umol, 69.72 uL, 1 eq) and the solution was stirred at 25 °C for 1 h. The solution was blow dry to remove the DCM and give the residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1). (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-azabicyclo[3.2.0]heptane-2-carboxamide (165 mg, 597.10 umol, 84.57% yield, 100% purity) was obtained as yellow solid.

Step 3: (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.2.0]heptane-2-carboxamide

[0001362] To a solution of N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-azabicyclo[3.2.0]heptane-2-carboxamide (165.00 mg, 597.10 umol, 1 eq), 4-methoxy-1H-indole-2-carboxylic acid (171.23 mg, 895.66 umol, 1.5 eq) in DCM (2 mL) was added the T_3P (284.98 mg, 895.66 umol, 266.34 uL, 1.5 eq), DIEA (154.34 mg, 1.19 mmol, 208.01 uL, 2 eq), the solution was stirred at 25 °C for 1 h. Upon completion, the solution was diluted with H_2O (20 mL), extracted with ethyl acetate (30 mL * 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-HPLC (neutral condition).

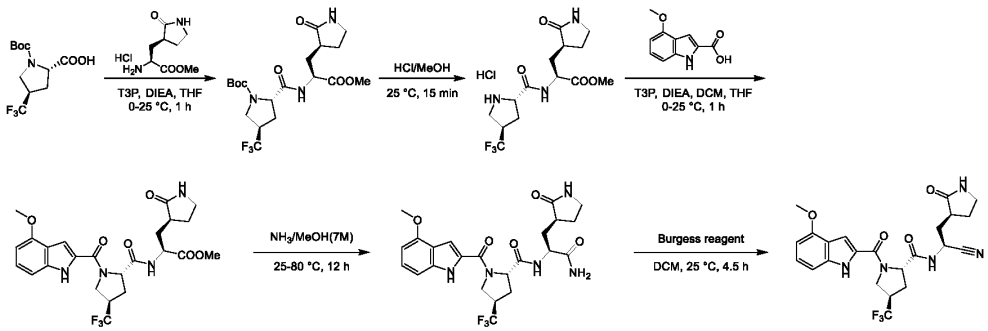
[0001363] Column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN];B%: 25%-45%,8 min.

[0001364] (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.2.0]heptane-2-carboxamide (98 mg, 218.02 umol, 36.51% yield, 100% purity) was obtained as white solid. ^1H NMR (400MHz, DMSO-d6) δ = 11.57 (br s, 1H), 8.79 (br d, J=7.4 Hz, 1H), 7.69 (br s, 1H), 7.17 - 6.95 (m, 3H), 6.52 (br d, J=7.3 Hz, 1H), 4.97 (br d, J=6.8 Hz, 1H), 4.63 (br d, J=8.2 Hz, 1H), 4.33 - 3.97 (m,

2H), 3.89 (br s, 3H), 3.28 - 2.79 (m, 4H), 2.30 - 1.55 (m, 9H). MS (ESI) m/z 450.3 [M+H]+.

[0001365] (1R,2R,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.2.0]heptane-2-carboxamide (23 mg, 51.17 umol, 8.57% yield, 100% purity) was obtained as white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 11.56 (br s, 1H), 9.13 - 8.71 (m, 1H), 7.83 - 7.44 (m, 1H), 7.23 - 6.89 (m, 3H), 6.77 - 6.36 (m, 1H), 5.18 - 4.57 (m, 2H), 4.32 - 3.94 (m, 2H), 3.92 - 3.74 (m, 3H), 3.71 - 3.40 (m, 1H), 3.23 - 2.76 (m, 3H), 2.32 - 1.47 (m, 9H). MS (ESI) *m/z* 450.3 $[M+H]^+$.

Example 168. Synthesis of viral protease inhibitor compound 549



Step 1: tert-butyl (2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl] carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate

[0001366] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (283.01 mg, 1.27 mmol, 1.2 *eq*, HCl) and (2S,4R)-1-tert-butoxycarbonyl-4-(trifluoromethyl)pyrrolidine-2-carboxylic acid (300 mg, 1.06 mmol, 1 *eq*), DIEA (684.44 mg, 5.30 mmol, 922.43 uL, 5 *eq*) in THF (3 mL) was added T_3P (1.01 g, 1.59 mmol, 944.87 uL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 1 h. Upon completion, the residue was poured into saturated sodium bicarbonate solution (10 mL) and stirred for 1 min. The aqueous phase was extracted with ethyl acetate (10 mL * 2). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give Tert-butyl(2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate (0.5 g, crude) as light yellow oil and used directly next step. MS (ESI) *m/z* 452.1 $[M+H]^+$.

Step 2: methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(2S,4R)-4-(trifluoromethyl)pyrrolidine-2- carbonyl]amino]propanoate

[0001367] To a mixture of tert-butyl (2S,4R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl]carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate (0.5 g, 1.11 mmol, 1 *eq*) was added HCl/MeOH (4 M, 3 mL, 10.83 *eq*) at 25 °C under N_2. The mixture was stirred at 25 °C for 15 min. Upon completion, the reaction mixture was concentrated to get the crude product Methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl] -2-[[(2S,4R)-4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]propanoate (450 mg, crude, HCl) as the light yellow oil. MS (ESI) *m/z* 352.1 $[M+H]^+$.

Step 3: methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2- carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001368] To a mixture of methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(2S,4R)-4-(trifluoromethyl) pyrrolidine-2-carbonyl]amino]propanoate (395.52 mg, 1.02 mmol, 1.3 *eq*, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (150 mg, 784.59 umol, 1 *eq*) and DIPEA (507.01 mg, 3.92 mmol, 683.31 uL, 5 *eq*) in THF (3 mL) and DCM (3 mL) was added T_3P (748.92 mg, 1.18 mmol, 699.93 uL, 50% purity, 1.5 *eq*) at 0 °C under N_2. The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was poured into saturated sodium bicarbonate solution (5 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (5 mL * 2). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by prep-TLC (dichloromethane:methanol = 10:1, R_f = 0.43) to give methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl) -4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, crude) as a light yellow solid. MS (ESI) *m/z* 525.2 $[M+H]^+$.

Step 4: (2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-(nitrosomethyl)-2-[(3S)-2-oxopyrr olidin-3-yl]ethyl]-4-(trifluoromethyl)pyrrolidine-2-carboxamide

[0001369] To a mixture of methyl (2S)-2-[[(2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-4- (trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (250 mg, 476.65 umol, 1 *eq*) was added NH_3/MeOH (7 M, 3 mL, 44.06 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 80 °C for 12 h. Upon

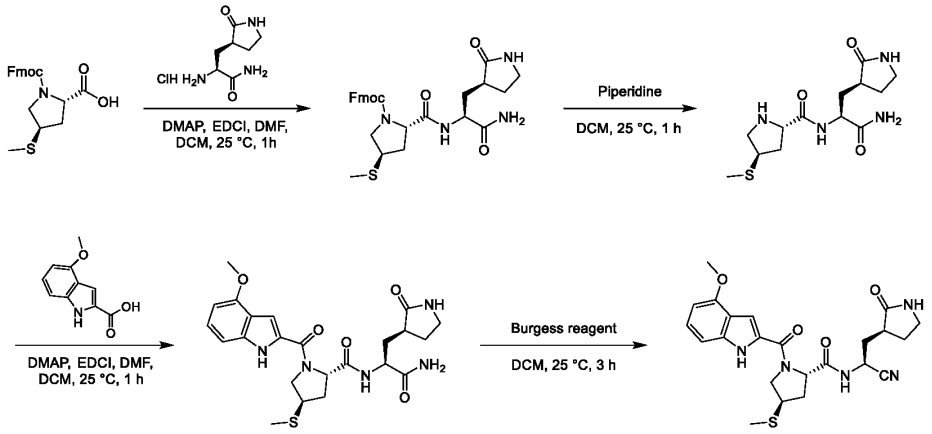
completion, the reaction mixture was cooled to 25 °C and concentrated to get the crude product. The crude product was purified by prep-TLC (dichloromethane: methanol = 10:1, Rf = 0.3) to give (2S,4R)-1-(4-methoxy- 1H-indole-2-carbonyl)-N-[(1S)-1-(nitrosomethyl)-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-(trifluoromethyl)pyrrolidine-2-carboxamide (130 mg, 247.51 umol, 51.93% yield, 97% purity) as a light yellow solid. MS (ESI) *m/z* 510.2 $[M+H]^+$.

Step 5: (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2- carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide

[0001370] To a mixture of (2S,4R)-1-(4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-(nitrosomethyl)-2-[(3S) -2-oxopyrrolidin-3-yl]ethyl]-4-(trifluoromethyl)pyrrolidine-2-carboxamide (120 mg, 235.54 umol, 1 *eq*) in DCM (6 mL) was added Burgess reagent (112.26 mg, 471.07 umol, 2 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 4.5 h. Upon completion, the residue was poured into water (0.5 mL) and stirred for 10 min. Then the reaction mixture was concentrated to get the crude product. The crude product was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN];B%: 25%-45%,8 min) to give (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopy rrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide (22.56 mg, 45.90 umol, 19.49% yield, 100% purity) as a white solid. MS (ESI) *m/z* 492.2 $[M+H]^+$.

[0001371] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.12 - 7.21 (m, 1 H), 6.84 - 7.10 (m, 2 H), 6.50 (br s, 1 H), 4.94 - 5.26 (m, 1 H), 4.75 (br s, 1 H), 4.07 - 4.47 (m, 2 H), 3.79 - 4.01 (m, 3 H), 3.45 (br s, 1 H), 2.16 - 2.98 (m, 6 H), 1.62 - 2.02 (m, 2 H), 1.39 (br s, 1 H)

Example 169. Synthesis of viral protease inhibitor compound 551



Step 1: 9H-fluoren-9-ylmethyl (2S,4R)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl] methyl]ethyl]carbamoyl]-4-methylsulfanyl-pyrrolidine-1-carboxylate

[0001372] To a mixture (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanamide (200.57 mg, 782.35 umol, 81% purity, 1 eq, HCl) and (2S,4R)-1-(9H-fluoren-9-ylmethoxycarbonyl)- 4-methylsulfanyl-pyrrolidine-2-carboxylic acid (300 mg, 782.35 umol, 1 eq) in DCM (4 mL) and DMF (2 mL) was added EDCI (299.96 mg, 1.56 mmol, 2 eq) and DMAP (191.16 mg, 1.56 mmol, 2 eq) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C and stirred for 1 hours. Upon completion. The aqueous phase was extracted with ethyl acetate (30 mL * 3) and H_2O (40 mL).The combined organic phase was washed with brine (30 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. To afford 9H-fluoren-9-ylmethyl (2S,4R)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-methylsulfanyl-pyrrolidine-1-carboxylate (180 mg, 322.00 umol, 41.16% yield, 96% purity) as white solid. MS (ESI) *m/z* 537.3 $[M+H]^+$

Step 2: (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4-methylsulfanyl- pyrrolidine-2-carboxamide

[0001373] To a mixture of 9H-fluoren-9-ylmethyl (2S,4R)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-4-methylsulfanyl-pyrrolidine-1-carboxylate (180 mg, 335.42 umol, 1 eq) in DCM (2 mL) was added piperidine (344.88 mg, 4.05 mmol, 0.4 mL, 12.08 eq) in one portion at 20 °C. The mixture was stirred at 20 °C for 1 h. Upon completion. The crude was purified by pre-TLC (SiO_2, DCM/MEOH = 5/1). To afford (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-

yl]methyl]ethyl]-4- methylsulfanyl- pyrrolidine-2-carboxamide (80 mg, 127.23 umol, 37.93% yield, 50% purity) as a white solid.

[0001374] ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.15 (br d, J=9.6 Hz, 1H), 7.63 (s, 1H), 7.53 (s, 1H), 7.12 (br s, 1H), 4.28 (br s, 1H), 3.73 (br t, J=7.2 Hz, 1H), 3.22 - 3.03 (m, 4H), 2.99 (br s, 2H), 2.78 (br d, J=7.2 Hz, 1H), 2.28 - 1.86 (m, 8H), 1.74 - 1.43 (m, 6H).

Step 3: (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methylsulfanyl-pyrrolidine-2-carboxamide

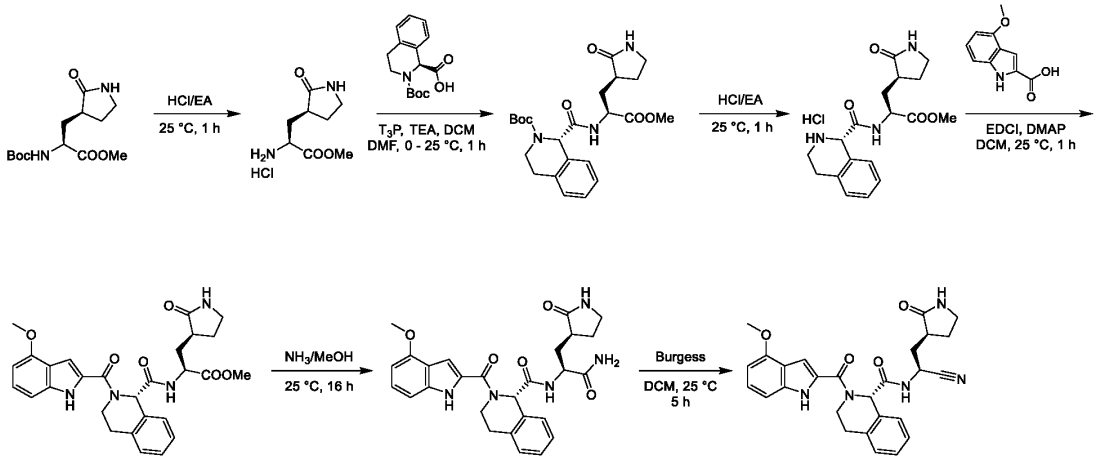
[0001375] To a mixture of (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-4- methylsulfanyl-pyrrolidine-2-carboxamide (80 mg, 254.45 umol, 1 eq) and 4-methoxy-1H-indole-2-carboxylic acid (48.65 mg, 254.45 umol, 1 eq) in DCM (2 mL) and DMF (1 mL) was added EDCI (97.56 mg, 508.90 umol, 2 eq) and DMAP (62.17 mg, 508.90 umol, 2 eq) in one portion at 20 °C and stirred for 1h. Upon completion, the mixture was dried by N_2. The crude was purified by pre-HPLC, column: Phenomenex Gemini-NX C18 75*30 mm*3um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 25%-45%,8 min. To afford (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methylsulfanyl-pyrrolidine-2-carboxamide (80 mg, 164.08 umol, 64.48% yield, 100% purity) as white solid. MS (ESI) *m/z* 488.3 $[M+H]^+$

Step 4: (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methylsulfanyl-pyrrolidine-2-carboxamide

[0001376] To a mixture of (2S,4R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-1- (4-methoxy-1H-indole-2-carbonyl)-4-methylsulfanyl-pyrrolidine-2-carboxamide (80 mg, 164.08 umol, 1 eq) in DCM (4 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (312.81 mg, 1.31 mmol, 8 eq) in one portion at 20 °C and stirred for 3 h. Upon completion. The crude was dried by N_2. The crude was purified by pre-HPLC, column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 15%-45%,10 min. To afford (2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-methylsulfanyl-pyrrolidine-2-carboxamide (31.9 mg, 67.94 umol, 41.40% yield, 100% purity) as white solid. MS (ESI) *m/z* 470.2 $[M+H]^+$

[0001377] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.38 (br s, 1H), 8.85 (br s, 1H), 7.46 (br s, 1H), 7.17 - 7.09 (m, 1H), 7.09 - 7.02 (m, 1H), 6.91 (br s, 1H), 6.52 (d, J=7.5 Hz, 1H), 4.95 (br d, J=7.1 Hz, 1H), 4.86 - 4.60 (m, 1H), 4.27 (br s, 1H), 3.90 (s, 4H), 3.54 (br s, 1H), 3.18 - 3.12 (m, 2H), 2.50-2.39 (br s, 8H), 1.89 - 1.61 (m, 2H).

Example 170. Synthesis of viral protease inhibitor compound 555



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001378] A solution of methyl (2*S*)-2-(tert-butoxycarbonylamino)-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (300 mg, 1.05 mmol, 1 *eq*) and HCl/EA (3 mL) was stirred at 25 °C for 0.5 h. Upon completion, the residue was concentrated under reduced pressure to get the product methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (200 mg, crude, HCl) as white solid MS (ESI) *m/z* 187.1 $[M+H]^+$.

Step 2: tert-butyl (1S)-1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] carbamoyl]-3,4-dihydro-1H-isoquinoline-2-carboxylate

[0001379] A solution of methyl (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 898.19 umol, 1 *eq*, HCl), (1S)-2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinoline-1-carboxylic acid (249.08 mg, 898.19 umol, 1 *eq*) and TEA (454.44 mg, 4.49 mmol, 625.09 uL, 5 *eq*) in DCM (2 mL) and DMF (1 mL) was cooled to 0 °C. After adding T_3P (1.71 g, 2.69 mmol, 1.60 mL, 50% purity, 3 *eq*) at 0 °C, the mixture was stirred for 1 h and warmed to 25 °C gradually. Upon completion, the mixture was added H_2O (30 mL) and then extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated

under reduced pressure to get the product tert-butyl (1*S*)-1-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylate (300 mg, crude) as a yellow solid. MS (ESI) *m/z* 446.2 $[M+H]^+$.

Step 3: methyl (2S)-3-[(3S)-2-oxopyrrolidin-3-yl]-2-[[(1S)-1,2,3,4-tetrahydroisoquinoline-1-carbonyl]amino]propanoate

[0001380] A solution of tert-butyl (1*S*)-1-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylate (300 mg, 673.39 umol, 1 *eq*) in HCl/EA (4 M) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product methyl(2*S*)-3-[(3*S*)-2-oxopyrrolidin-3-yl]-2-[[(1*S*)-1,2,3,4-tetrahydroisoquinoline-1-carbonyl]amino]propanoate (210 mg, crude) as white solid. MS (ESI) *m/z* 346.2 $[M+H]^+$.

Step 4: methyl (2S)-2-[[(1S)-2-(4-methoxy-1H-indole-2-carbonyl)-3,4-dihydro-1H-isoquinoline-1-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001381] A solution of methyl (2*S*)-3-[(3*S*)-2-oxopyrrolidin-3-yl]-2-[[(1*S*)-1,2,3,4-tetrahydroisoquinoline-1-carbonyl]amino]propanoate (190 mg, 497.57 umol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (95.13 mg, 497.57 umol, 1 *eq*), EDCI (286.16 mg, 1.49 mmol, 3 *eq*) and DMAP (182.36 mg, 1.49 mmol, 3 *eq*) in DCM (4 mL) was stirred at 25 °C for 1 h. Upon completion, the mixture was added H_2O (30 mL) and then extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 * 30 mm * 3 um; mobile phase: [water (0.05% NH_3H_2O + 10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 8 min) to get the product methyl (2*S*)-2-[[(1*S*)-2-(4-methoxy-1*H*-indole-2-carbonyl)-3,4-dihydro-1*H*-isoquinoline-1-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (40.1 mg, 73.46 umol, 14.76% yield, 95% purity) as a white solid. MS (ESI) *m/z* 519.2 $[M+H]^+$.

Step 5: (1S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-3,4-dihydro-1H-isoquinoline-1-carboxamide

[0001382] A solution of methyl (2*S*)-2-[[(1*S*)-2-(4-methoxy-1*H*-indole-2-carbonyl)-3,4-dihydro-1*H*-isoquinoline-1-carbonyl]amino]-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanoate (40

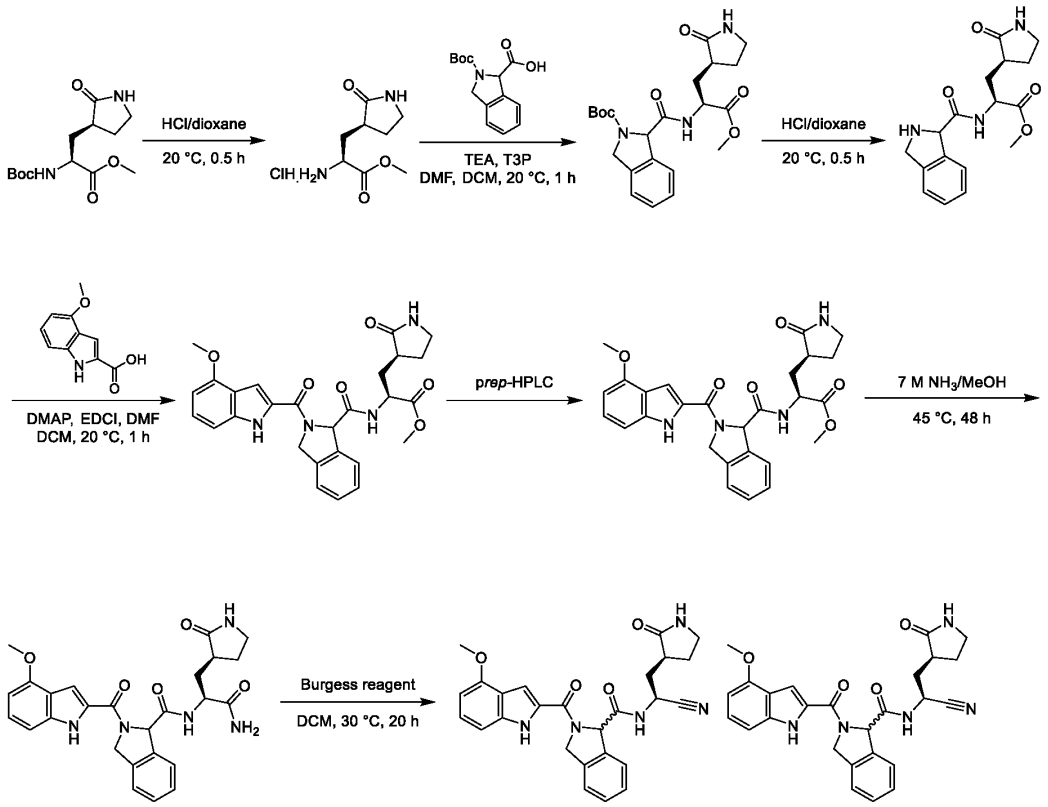
mg, 77.14 umol, 1 *eq*) and NH_3/MeOH (7 M, 10 mL, 907.48 *eq*) was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to afford (1*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-3,4-dihydro-1*H*-isoquinoline-1-carboxamide (35 mg, crude) as a yellow solid. MS (ESI) *m/z* 504.2 $[M+H]^+$.

Step 6: (1S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-3,4-dihydro-1H-isoquinoline-1-carboxamide

[0001383] A solution of (1*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-3,4-dihydro-1H-isoquinoline-1-carboxamide (35 mg, 69.51 umol, 1 *eq*) and methoxycarbonyl-(triethylammonio)sulfonyl-azanide (82.82 mg, 347.53 umol, 5 *eq*) in DCM (5 mL) was stirred at 25 °C for 5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 * 30 mm * 3 um; mobile phase: [water (0.05% NH_3H_2O + 10 mM NH_4HCO_3) - ACN]; B%: 20% - 50%, 8 min) to get the product (1*S*)-N-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1*H*-indole-2-carbonyl)-3,4-dihydro-1*H*-isoquinoline-1-carboxamide (6 mg, 12.08 umol, 17.38% yield, 97.74% purity) as white solid. MS (ESI) *m/z* 486.2 $[M+H]^+$.

[0001384] ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.57 - 7.47 (m, 1H), 7.40 - 7.25 (m, 1H), 7.12 - 7.11 (m, 1H), 7.10 - 6.99 (m, 2H), 6.59 - 6.50 (m, 1H), 6.82 - 6.61 (m, 1H), 5.67 (s, 1H), 5.03 - 4.96 (m, 1H), 4.46 (s, 1H), 4.05 - 3.95 (m, 1H), 3.94 - 3.86 (m, 3H), 3.37 - 3.32 (m , 1H), 3.28 - 3.16 (m, 2H), 3.05 - 2.90 (m, 2H), 2.62 (s, 1H), 2.44 - 2.20 (m, 2H), 1.98 - 1.67 (m, 2H)

Example 171. Synthesis of viral protease inhibitor compound 557



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate hydrochloride

[0001385] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (500 mg, 1.75 mmol, 1 *eq*) in HCl/dioxane (4 M, 8.73 mL, 20 *eq*) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 0.5 h under N_2 atmosphere. Upon completion, the reaction mixture was concentrated under reduced pressure to afford methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (630 mg, crude, HCl) as yellow oil. MS (ESI) *m/z* 223.2 $[M+H]^+$.

Step 2: tert-butyl 1-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)isoindoline-2-carboxylate

[0001386] To a solution of 2-tert-butoxycarbonylisoindoline-1-carboxylic acid (436.93 mg, 1.66 mmol, 1 *eq*) methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (630 mg, 1.74 mmol, 61.58% purity, 1.05 *eq*, HCl) in DCM (5 mL) and DMF (5 mL) was added T_3P (1.58 g, 2.49 mmol, 1.48 mL, 50% purity, 1.5 *eq*) and TEA (1.01 g, 9.96 mmol, 1.39 mL, 6 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction

mixture was quenched by addition H_2O (20 mL), and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to get the product tert-butyl 1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]isoindoline-2-carboxylate (720 mg, crude) as a white solid. MS (ESI) *m/z* 432.2 $[M+H]^+$.

Step 3: (2S)-methyl 2-(isoindoline-1-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001387] A mixture of tert-butyl 1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]isoindoline-2-carboxylate (720 mg, 1.67 mmol, 1 *eq*) in HCl/dioxane (4 M, 8.34 mL, 20 *eq*) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 0.5 h under N_2 atmosphere. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product methyl (2S)-2-(isoindoline-1-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (770 mg, crude, HCl) as a brown oil. MS (ESI) *m/z* 332.3$[M+H]^+$.

Step 4: (2S)-methyl 2-(2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001388] A mixture of 4-methoxy-1H-indole-2-carboxylic acid (287.43 mg, 1.50 mmol, 1 *eq*), methyl (2S)-2-(isoindoline-1-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (770 mg, 1.65 mmol, 79% purity, 1.1 *eq*, HCl), DMAP (367.34 mg, 3.01 mmol, 2 *eq*), EDCI (576.42 mg, 3.01 mmol, 2 *eq*) in DCM (8 mL) and DMF (2.7 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 1 h under N_2 atmosphere. Upon completion, the reaction mixture was quenched by addition H_2O (25 mL), and then extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by neutral *prep*-HPLC (column: Kromasil C18 (250*50 mm*10 um); mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 25%-45%, 10 min) to get the product methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (Isomer 1: 150 mg, 297.30 umol, 19.78% yield) as a white solid. MS (ESI) *m/z* 505.3$[M+H]^+$.

[0001389] To get methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (Isomer 2: 140 mg, 277.48 umol, 18.46% yield) as white solid. MS (ESI) m/z 505.3[M+H]+.

Step 5.1: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide

[0001390] A solution of methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 297.30 umol, 1 *eq*) in MeOH/NH_3 (7 M, 849.44 uL, 20 *eq*) was stirred at 45 °C for 48 h. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl] ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (130 mg, crude) as a colorless oil. MS (ESI) *m/z* 490.3$[M+H]^+$.

Step 5.2: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide

[0001391] A solution of methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carbonyl] amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (140 mg, 277.48 umol, 1 *eq*) in MeOH/NH_3 (7 M, 792.81 uL, 20 *eq*) was stirred at 45 °C for 24 h. Upon completion, the reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (110 mg, crude) as a colorless oil. MS (ESI) *m/z* 490.3$[M+H]^+$.

Step 6.1: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide

[0001392] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (125 mg, 255.35 umol, 1 *eq*) in DCM (8 mL) was added Burgess reagent (273.84 mg, 1.15 mmol, 4.5 *eq*). The mixture was stirred at 30 °C for 20 h. Upon completion, the reaction mixture was quenched by addition H_2O (0.5 mL), and then concentrated under reduced pressure to give a residue. The residue was purified by neutral *prep*-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 20%-50%,10 min) to get the product N-[(1S)-1-cyano-2-[(3S)-2-

oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (31.50 mg, 66.81 umol, 26.16% yield, 100% purity) as a white solid. MS (ESI) *m/z* 472.3$[M+H]^+$.

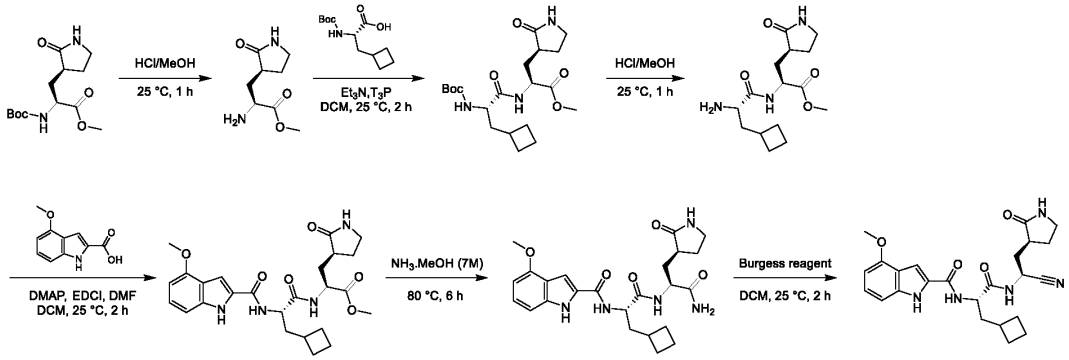
[0001393] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.53 - 11.83 (m, 1 H) 9.11 - 9.78 (m, 1 H) 7.31 - 7.78 (m, 5 H) 6.95 - 7.29 (m, 3 H) 6.42 - 6.63 (m, 1 H) 5.73 (s, 1 H) 5.27 - 5.41 (m, 1 H) 4.91 - 5.05 (m, 1 H) 3.76 - 3.99 (m, 3 H) 2.71 - 3.19 (m, 2 H) 2.00 - 2.30 (m, 3 H) 1.20 - 1.87 (m, 2 H).

Step 6.2: N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide

[0001394] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl] -2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (105 mg, 214.49 umol, 1 *eq*) in DCM (6 mL) was added Burgess reagent (204.47 mg, 857.98 umol, 4 *eq*). The mixture was stirred at 30 °C for 7 h. Upon completion, the reaction mixture was quenched by addition H_2O (0.5 mL), and then concentrated under reduced pressure to give a residue. The residue was purified by neutral *prep*-HPLC (column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(10 mM NH4HCO3)-ACN];B%: 25%-55%,8 min) to get the product N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)isoindoline-1-carboxamide (34.83 mg, 73.72 umol, 34.37% yield, 99.791% purity) as a white solid. MS (ESI) *m/z* 472.3$[M+H]^+$.

[0001395] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.72 (s, 1 H) 9.19 (d, *J*=8.11 Hz, 1 H) 7.31 - 7.76 (m, 5 H) 6.92 - 7.29 (m, 3 H) 6.56 (d, *J*=7.75 Hz, 1 H) 5.74 (s, 1 H) 5.34 (br d, *J*=10.13 Hz, 1 H) 4.96 (q, *J*=8.23 Hz, 1 H) 3.86 - 3.89 (m, 1 H) 3.86 - 4.55 (m, 1 H) 3.84 - 4.01 (m, 3 H) 2.96 - 3.22 (m, 2 H) 2.25 - 2.41 (m, 1 H) 2.02 - 2.20 (m, 2 H) 1.47 - 1.87 (m, 2 H).

Example 172. Synthesis of viral protease inhibitor compound 577



Step 1: (S)-methyl 2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001396] To a solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (350 mg, 1.22 mmol, 1 eq) in MeOH (1 mL) was added drop-wise HCl/MeOH (4 M, 10 mL, 32.72 eq), and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to get methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (240 mg, crude, HCl) as a colourless oil. MS (ESI) *m/z* 187.1 $[M+H]^+$

Step 2: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclobutylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001397] A solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 898.19 umol, 1 eq, HCl) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclobutyl-propanoic acid (218.53 mg, 898.19 umol, 1 eq) in DCM (5 mL), and Et_3N (545.33 mg, 5.39 mmol, 750.11 uL, 6.0 eq) and T_3P (1.71 g, 2.69 mmol, 1.60 mL, 50% purity, 3.0 eq) were added. The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (40 mL) at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine 30 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate = 0/1) to get the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclobutyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 486.04 umol, 54.11% yield) was obtained as a white solid. MS (ESI) *m/z* 412.1 $[M+H]^+$

Step 3: (S)-methyl 2-((S)-2-amino-3-cyclobutylpropanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001398] To a solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclobutyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (180 mg, 437.43 umol, 1 eq) in MeOH (1 mL) was added drop-wise HCl/MeOH (4 M, 12.00 mL, 109.73 eq), and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford methyl (2S)-2-[[(2S)-2-amino-3-cyclobutyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, HCl) as a white solid. MS (ESI) *m/z* 312.2 $[M+H]^+$

Step 4: (S)-methyl 2-((S)-3-cyclobutyl-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001399] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclobutyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 431.24 umol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (82.45 mg, 431.24 umol, 1 eq) in DMF (1.5 mL) was added DMAP (105.37 mg, 862.47 umol, 2.0 eq), EDCI (165.34 mg, 862.47 umol, 2.0 eq) and DCM (6 mL). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (40 mL) at 0 °C, and extracted with DCM (20 mL * 3). The combined organic layers were washed with brine 30 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/ethyl acetate =0/1) to afford methyl (2S)-2-[[(2S)-3-cyclobutyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (120 mg, 247.66 umol, 57.43% yield) as a yellow oil. MS (ESI) *m/z* 485.2 $[M+H]^+$

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclobutyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001400] A solution of methyl (2S)-2-[[(2S)-3-cyclobutyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (100 mg, 206.38 umol, 1 eq) in NH_3/MeOH (7 M, 10 mL, 339.18 eq) was stirred at 80 °C for 6 h. The reaction mixture was concentrated under reduced pressure to afford N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclobutylmethyl)-

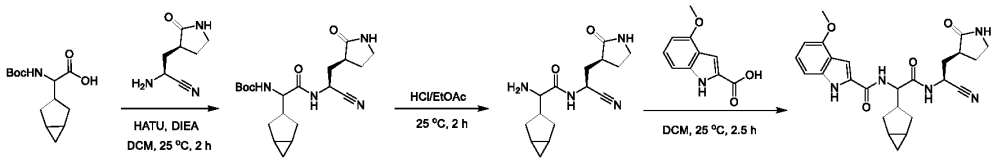
2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (90 mg, crude) as a yellow solid. MS (ESI) *m/z* 470.1 $[M+H]^+$

Step 7: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclobutyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001401] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclobutylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (90 mg, 191.68 umol, 1 eq) in DCM (2 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (228.40 mg, 958.40 umol, 5.0 eq), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30%-60%, 8 min) to afford N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclobutylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (18.04 mg, 39.95 umol, 20.84% yield, 100% purity) as a white solid. MS (ESI) *m/z* 452.3 $[M+H]^+$.

[0001402] ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.26 (d, J = 0.7 Hz, 1H), 7.11 - 7.18 (m, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 10.1, 5.9 Hz, 1H), 4.41 (dd, J = 8.6, 6.2 Hz, 1H), 3.93 (s, 3H), 3.25 - 3.30 (m, 2H), 2.61 (dd, J = 8.7, 5.3 Hz, 1H), 2.42 - 2.53 (m, 1H), 2.25 - 2.39 (m, 2H), 2.06 - 2.18 (m, 2H), 1.73 - 2.01 (m, 8H).

Example 173. Synthesis of viral protease inhibitor compound 589



Step 1: tert-butyl(1-(bicyclo[3.1.0]hexan-3-yl)-2-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-2-oxoethyl)carbamate

[0001403] A mixture of (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanenitrile (89.1 mg, 0.47 mmol, 1.2 *eq*, HCl), HATU (223.3 mg, 0.58 mmol, 1.5 *eq*) and DIEA (151.8 mg, 1.18 mmol, 0.20 mL, 3 *eq*) in DCM (2 mL) was stirred at 25 °C for 0.5 h, and then

2-(3-bicyclo[3.1.0]hexanyl)-2-(tert-butoxycarbonylamino)acetic acid (100 mg, 0.39 mmol, 1 *eq*) was added into the reaction. The resulting mixture was stirred 25 °C for 2 h. LCMS detected desired compound. The reaction mixture was added H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ethergradient @ 20 mL/min). Compound tert-butyl N-[1-(3-bicyclo[3.1.0]hexanyl)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-2-oxo-ethyl]carbamate (150 mg, 0.23 mmol, 58.8% yield, 60% purity) was obtained as colorless oil.

Step 2: 2-amino-2-(bicyclo[3.1.0]hexan-3-yl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)acetamide

[0001404] To a solution of tert-butyl N-[1-(3-bicyclo[3.1.0]hexanyl)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-2-oxo-ethyl]carbamate (140 mg, 0.21 mmol, 60% purity, 1 *eq*) in EtOAc (0.1 mL) was added HCl/EtOAc (4 M, 0.84 mL, 15.62 *eq*). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. It was used into next step without purification. Compound 2-amino-2-(3-bicyclo[3.1.0]hexanyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]acetamide (110 mg, crude, HCl) was obtained as a white solid.

Step 3: N-(1-(bicyclo[3.1.0]hexan-3-yl)-2-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-2-oxoethyl)-4-methoxy-1H-indole-2-carboxamide

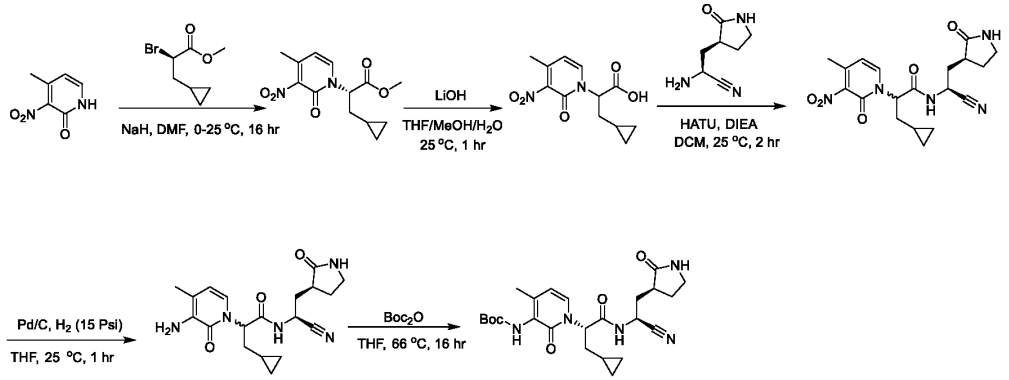
[0001405] A mixture of 4-methoxy-1H-indole-2-carboxylic acid (52.1 mg, 0.27 mmol, 1.2 *eq*), HATU (129.6 mg, 0.34 mmol, 1.5 *eq*) and DIEA (88.1 mg, 0.68 mol, 0.11 mL, 3 *eq*) in DCM (2 mL) was stirred at 25 °C for 0.5 h, and then 2-amino-2-(3-bicyclo[3.1.0]hexanyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]acetamide (110 mg, 0.22 mmol, 60% purity, 1 *eq*) was added into the reaction. The resulting mixture was stirred 25 °C for 2 h. TLC (petroleum ether/ethyl acetate = 0:1, UV 254) indicated starting material was consumed completely and new spots formed. LCMS detected desired compound. The reaction mixture was added H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (20 mL),

dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ethergradient @ 30 mL/min) to give 50 mg 46% of desire compound. Then it was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 25%-55%,9.5 min). Compound N-[1-(3-bicyclo[3.1.0]hexanyl)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (7 mg, 15.1 umol, 6.6% yield, 100% purity) was obtained as a white solid.

[0001406] LCMS: Rt = 0.813 min; for $C_{25}H_{29}N_5O_4$ MS Calcd.: 463.53; MS Found: 464.1 [$M+H^+$].

[0001407] ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 - 7.31 (m, 1 H), 7.11 - 7.18 (m, 1 H), 7.00 - 7.06 (m, 1 H), 6.51 (d, *J* = 7.63 Hz, 1 H), 4.93 - 5.01 (m, 2 H), 4.16 - 4.34 (m, 1 H), 3.93 (s, 3 H), 3.24 - 3.29 (m, 1 H), 2.45 - 2.67 (m, 1 H), 2.25 - 2.38 (m, 2 H), 2.00 - 2.17 (m, 2 H), 1.76 - 1.95 (m, 3 H), 1.60 - 1.71 (m, 1 H), 1.27 - 1.45 (m, 3 H), 0.74 (br d, *J* = 5.00 Hz, 1 H), 0.13 - 0.38 (m, 2 H).

Example 174. Synthesis of viral protease inhibitor compound 590



Step 2: Methyl (2S)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate

[0001408] To a solution of 4-methyl-3-nitro-1*H*-pyridin-2-one (1 g, 6.49 mmol, 1 *eq*) in DMF (15 mL) was added NaH (363.3 mg, 9.08 mmol, 60% purity, 1.4 *eq*) at 0 °C, and the reaction mixture was stirred at 25 °C for 0.5 h. Then, to the reaction was added methyl (2*R*)-2-bromo-3-cyclopropyl-propanoate (1.34 g, 6.49 mmol, 1 *eq*) at 0 °C.

The mixture was stirred at 25 °C for 16 h under N_2. The mixture was quenched with H_2O (20 mL), and extracted with ethyl acetate (50 mL * 3). The combined organic layers was washed with brine (40 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/petroleum ether gradient @ 35 mL/min) to give methyl (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate (867 mg, 47.4% yield) as a yellow solid.

[0001409] LCMS: Rt = 0.785 min; for $C_{13}H_{16}N_2O_5$ MS Calcd.: 280.11; MS Found: 281.1 [$M+H^+$].

Step 3: (2S)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid

[0001410] A mixture of methyl (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoate (867 mg, 3.09 mmol, 1 *eq*), $LiOH.H_2O$ (519.2 mg, 12.37 mmol, 4 *eq*) in THF (6 mL), MeOH (2 mL), H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 h under N_2 atmosphere. LCMS showed one peak with desired MS was detected. The mixture was added H_2O (5 mL), and then the mixture was added 2 M HCl (4 mL) to adjust the pH of the mixture to about 6~7. The mixture was extracted with ethyl acetate (30 mL * 3). The combined organic layers was washed with brine (20 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure to give (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid (791 mg, 94.8% yield) as a yellow solid.

[0001411] LCMS: Rt = 0.735 min; for $C_{12}H_{14}N_2O_5$ MS Calcd.: 266.09; MS Found: 267.0 [$M+H^+$].

Step 4: N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide

[0001412] To a solution of (2*S*)-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanoic acid (791 mg, 2.97 mmol, 1 *eq*) in DCM (10 mL) was added HATU (1.36 g, 3.57 mmol, 1.2 *eq*), DIPEA (1.15 g, 8.91 mmol, 1.55 mL, 3 *eq*) and (2*S*)-2-amino-3-[(3*S*)-2-oxopyrrolidin-3-yl]propanenitrile (676.0 mg, 3.57 mmol, 1.2 *eq*, HCl). The mixture was stirred at 25 °C for 2 h. The mixture was quenched with H_2O (20 mL) and extracted with DCM (40 mL * 3). The combined organic layers was washed

with brine (20 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH ethergradient @ 35 mL/min) to give *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide (838 mg, 64.5% yield) as a yellow oil.

[0001413] LCMS: Rt = 0.741 min; for $C_{19}H_{23}N_5O_5$ MS Calcd.: 401.17; MS Found: 402.1 [$M+H^+$].

Step 5: 2-(3-Amino-4-methyl-2-oxo-1-pyridyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide

[0001414] To a solution of *N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-2-(4-methyl-3-nitro-2-oxo-1-pyridyl)propanamide (838 mg, 2.09 mmol, 1 *eq*) in THF (10 mL) was added Pd/C (566.5 mg, 0.53 mmol, 10% purity). The mixture was stirred at 25 °C for 1 h under H_2. The mixture was filtered and concentrated under reduce pressure to give 2-(3-amino-4-methyl-2-oxo-1-pyridyl)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (616 mg, 1.43 mmol, 68.7% yield, 86.5% purity) as a white solid.

[0001415] LCMS: Rt = 0.703 min; for $C_{19}H_{25}N_5O_3$ MS Calcd.: 371.20; MS Found: 372.1 [$M+H^+$].

Step 6: tert-Butyl N-[1-[2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methyl-2-oxo-3-pyridyl]carbamate

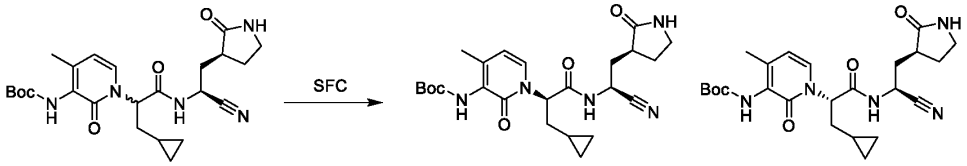
[0001416] A mixture of 2-(3-amino-4-methyl-2-oxo-1-pyridyl)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-3-cyclopropyl-propanamide (100 mg, 0.26 mmol, 1 *eq*) in Boc_2O (1 mL) and THF (1 mL), and then the mixture was stirred at 66 °C for 16 h under N_2 atmosphere. The mixture was concentrated under reduce pressure. The mixture was quenched with H_2O (20 mL), and extracted with ethyl acetate (30 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80 * 40 mm * 3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 26%-56%,7.8 min) to give *tert*-butyl *N*-[1-[2-[[(1*S*)-1-cyano-

2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methyl-2-oxo-3-pyridyl]carbamate (44.33 mg, 33.5% yield) as a white solid.

[0001417] LCMS: Rt = 0.798 min; for $C_{34}H_{51}N_5O_{10}$ MS Calcd.: 471.55; MS Found: 472.2 [M+H$^+$].

[0001418] ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (dd, *J*=1.5, 7.3 Hz, 1H), 6.36 - 6.27 (m, 1H), 5.56 - 5.35 (m, 1H), 5.18 - 4.97 (m, 1H), 3.35 - 3.32 (m, 1H), 3.29 - 3.25 (m, 1H), 2.52 (tq, *J*=4.8, 9.3 Hz, 1H), 2.45 - 2.22 (m, 2H), 2.18 (d, *J*=5.0 Hz, 3H), 2.06 - 1.92 (m, 2H), 1.91 - 1.71 (m, 2H), 1.48 (d, *J*=2.5 Hz, 9H), 0.69 - 0.56 (m, 1H), 0.50 - 0.37 (m, 2H), 0.19 - 0.01 (m, 2H).

Example 175. Synthesis of viral protease inhibitor compound 591



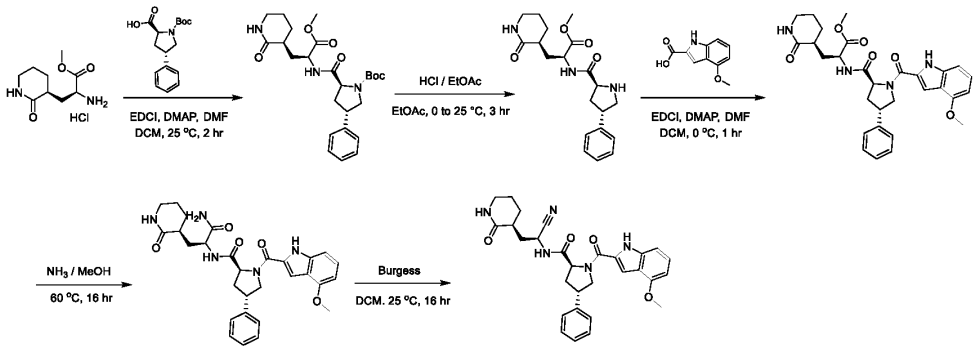
[0001419] *tert*-Butyl *N*-[1-[2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methyl-2-oxo-3-pyridyl]carbamate (42 mg, 89.0 umol, 1 eq) was further separated by SFC (condition: column: DAICEL CHIRALPAK AD(250 mm * 30 mm, 10 um);mobile phase: [0.1% NH_3H_2O ETOH];B%: 45%-45%, min) to afford *tert*-butyl *N*-[1-[(1*R*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methyl-2-oxo-3-pyridyl]carbamate (8.32 mg, 19.8% yield) as a white solid.

[0001420] Isomer 1: LCMS: Rt = 0.803 min; for $C_{34}H_{51}N_5O_{10}$ MS Calcd.: 471.55; MS Found: 472.2 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (d, *J*=7.3 Hz, 1H), 6.32 (d, *J*=7.3 Hz, 1H), 5.50 (t, *J*=7.8 Hz, 1H), 5.01 (dd, *J*=7.0, 9.0 Hz, 1H), 3.35 - 3.32 (m, 1H), 2.56 - 2.45 (m, 1H), 2.42 - 2.23 (m, 2H), 2.19 (s, 3H), 2.00 - 1.92 (m, 2H), 1.92 - 1.78 (m, 2H), 1.49 (s, 9H), 0.65 - 0.55 (m, 1H), 0.46 - 0.36 (m, 2H), 0.20 - 0.01 (m, 2H).

[0001421] Isomer 2: LCMS: Rt = 0.794 min; for $C_{34}H_{51}N_5O_{10}$ MS Calcd.: 471.55; MS Found: 472.2 [M+H$^+$]. ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (d, *J*=7.0 Hz, 1H), 6.31 (d, *J*=7.3 Hz, 1H), 5.41 (t, *J*=7.8 Hz, 1H), 5.10 - 4.97 (m, 1H), 3.30 - 3.25 (m, 2H), 2.52 (dq,

J=5.5, 9.2 Hz, 1H), 2.33 - 2.19 (m, 2H), 2.18 (s, 3H), 2.05 - 1.90 (m, 2H), 1.89 - 1.71 (m, 2H), 1.48 (s, 9H), 0.70 - 0.58 (m, 1H), 0.52 - 0.35 (m, 2H), 0.20 - 0.04 (m, 2H).

Example 176. Synthesis of viral protease inhibitor compound 611



Step 1: tert-Butyl (2S,4S)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl] ethyl]carbamoyl]-4-phenyl-pyrrolidine-1-carboxylate

[0001422] To a solution of (2*S*,4*S*)-1-tert-butoxycarbonyl-4-phenyl-pyrrolidine-2-carboxylic acid (100 mg, 0.34 mmol, 1 *eq*) and DMAP (125.8 mg, 1.03 mmol, 3 *eq*) in DCM (0.7 mL) was added EDCI (78.9 mg, 0.41 mmol, 1.2 *eq*), and then a solution of methyl (2*S*)-2-amino-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (81.2 mg, 0.34 mmol, 1 *eq*, HCl) in DMF (0.7 mL) was added. The reaction mixture was stirred at 25 °C for 2 h. LCMS showed one peak with desired MS was detected. The mixture was quenched with H_2O (10 mL), and extracted with ethyl acetate (20 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @ 30 mL/min) to give tert-butyl (2*S*,4*S*)-2-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-4-phenyl-pyrrolidine-1-carboxylate (100 mg, 60.4% yield) as a white solid.

[0001423] LCMS： Rt = 0.826 min; for $C_{25}H_{35}N_3O_6$ MS Calcd.: 473.25; MS Found: 474.1 [$M+H^+$].

Step 2: Methyl (2S)-3-[(3S)-2-oxo-3-piperidyl]-2-[[(2S,4S)-4-phenylpyrrolidine-2-carbonyl]amino]propanoate

[0001424] A mixture of tert-butyl (2*S*,4*S*)-2-[[(1*S*)-2-methoxy-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-4-phenyl-pyrrolidine-1-carboxylate (90 mg, 0.17 mmol, 1 *eq*, HCl) in 2 M HCl/EtOAc (6 mL), and then the mixture was stirred at 25 °C for 3 h under N_2 atmosphere. LCMS showed one peak with desired MS was detected. The mixture was concentrated under reduce pressure to give methyl (2*S*)-3-[(3*S*)-2-oxo-3-piperidyl]-2-[[(2*S*,4*S*)-4-phenylpyrrolidine-2-carbonyl]amino]propanoate (70 mg, 83.3% yield, HCl) was obtained as a yellow solid.

Step 3: Methyl (2S)-2-[[(2S,4S)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001425] To a solution of 4-methoxy-1*H*-indole-2-carboxylic acid (40.5 mg, 0.21 mmol, 1.5 *eq*) and DMAP (51.8 mg, 0.42 mmol, 3 *eq*) in DCM (0.5 mL) was added EDCI (32.5 mg, 0.16 mmol, 1.2 *eq*), and then a solution of methyl (2*S*)-3-[(3*S*)-2-oxo-3-piperidyl]-2-[[(2*S*,4*S*)-4-phenylpyrrolidine-2-carbonyl]amino]propanoate (58 mg, 0.14 mmol, 1 *eq*, HCl) in DMF (0.5 mL) was added. The reaction mixture was stirred at 0 °C for 1 h. LCMS showed one peak with desired MS was detected. The mixture was quenched with H_2O (20 mL) and then extracted with ethyl acetate (30 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @ 30 mL/min) to give methyl (2*S*)-2-[[(2*S*,4*S*)-1-(4-methoxy-1*H*-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (30 mg, 36.6% yield) as a white solid.

[0001426] LCMS: Rt = 1.730 min; for $C_{30}H_{34}N_4O_6$ MS Calcd.: 546.25; MS Found: 547.1 [$M+H^+$].

Step 4: (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carboxamide

[0001427] To a solution of methyl (2S)-2-[[(2S,4S)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (30 mg, 54.8 umol, 1 eq) and NH3 (7 M, 6 mL, 765.2 eq) and MeOH (6 mL) in sealed tube. The mixture was stirred at 60 °C for 16 h. LCMS showed one peak with desired MS was

detected. The mixture was concentrated under reduce pressure to give compound (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-1-(4-methoxy-1*H*-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carboxamide (29 mg, 99.40% yield) as a yellow solid.

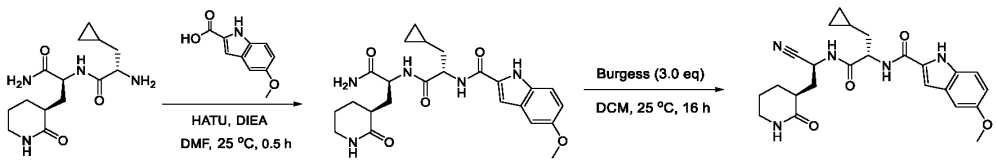
Step 5: (2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carboxamide

[0001428] To a solution of (2*S*,4*S*)-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-1-(4-methoxy-1*H*-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carboxamide (29 mg, 54.5 umol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (39.0 mg, 0.16 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 hr. LCMS showed one peak with desired MS was detected. The mixture was quenched with H_2O (5 mL), and extracted with ethyl acetate (10 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by *prep*-HPLC (column: Welch Xtimate C18 150 * 25 mm * 5 um; mobile phase: [water(0.225% FA)-ACN]; B%: 37%-67%,9.5 min) to give compound (2*S*,4*S*)-*N*-[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]-1-(4-methoxy-1*H*-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carboxamide (1.9 mg, 6.6% yield) as a white solid.

[0001429] LCMS： Rt = 1.730 min; for $C_{30}H_{34}N_4O_6$ MS Calcd.: 546.25; MS Found: 547.1 [$M+H^+$].

[0001430] ^1H NMR (400 MHz, CD_3OD) δ 7.38 - 7.31 (m, 1H), 7.30 - 7.23 (m, 4H), 7.19 - 7.13 (m, 1H), 7.10 - 7.04 (m, 1H), 6.95 (d, *J*=8.5 Hz, 1H), 6.41 (br d, *J*=7.5 Hz, 1H), 5.17 - 5.02 (m, 1H), 4.43 - 4.20 (m, 1H), 3.96 - 3.76 (m, 4H), 3.74 - 3.41 (m, 1H), 3.18 - 3.11 (m, 1H), 3.01 - 2.55 (m, 2H), 2.51 - 2.20 (m, 3H), 2.15 - 1.62 (m, 4H), 1.55 - 1.27 (m, 2H).

Example 177. Synthesis of viral protease inhibitor compound 619



Step 1: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1H-indole-2-carboxamide

[0001431] To a solution of (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (120.0 mg, 0.40 mmol, 1 *eq*) and 5-methoxy-1H-indole-2-carboxylic acid (77.4 mg, 0.40 mmol, 1 *eq*) DMF (2 mL) was added HATU (184.7 mg, 0.48 mmol, 1.2 *eq*) and DIEA (104.6 mg, 0.8 mmol, 0.14 mL, 2 *eq*). The mixture was stirred at 25 °C for 0.5 h, and then the reaction mixture was concentrated under reduced pressure to remove DMF. The residue was diluted with H_2O (10 mL) and extracted with ethyl acetate (25 mL * 3). The combined organic layers were washed with Brine (10 mL* 3）, dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol/Dichloromethane@ 20 mL/min). Compound *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1H-indole-2-carboxamide (180.0 mg, 94.6% yield) was obtained as a white solid.

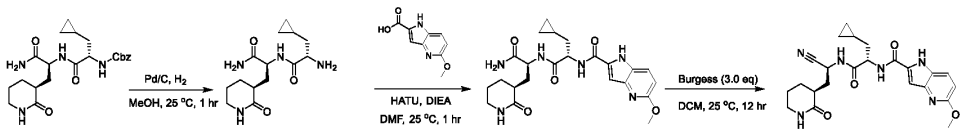
Step 2: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1H-indole-2-carboxamide

[0001432] To a solution of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1*H*-indole-2-carboxamide (180.0 mg, 0.38 mmol, 1 *eq*) in DCM (0.5 mL) was added Burgess reagent (274.0 mg, 1.15 mmol, 3 *eq*) at 0 °C. After the mixture was stirred at 25 °C for 16 h, the reaction mixture was concentrated under reduced pressure to remove DCM. The residue was diluted with H_2O (5 mL) and extracted with DCM (10 mL *3). The combined organic layers were washed with Brine (5 mL*3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 24%-54%, 7.8 min). Compound *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1*H*-indole-2-carboxamide (37.3 mg, 82.6 umol, 5.4 yield) was obtained as a white solid.

[0001433] LCMS: Rt = 0.785 min; for $C_{24}H_{29}N_5O_4$ MS Calcd.: 451.52; MS Found: 452.1 [$M+H^+$].

[0001434] ^1H NMR (400 MHz, CD_3OD) δ 7.32 (d, *J*=8.8 Hz, 1H), 7.13 - 7.06 (m, 2H), 6.89 (dd, *J*=2.4, 8.9 Hz, 1H), 5.16 - 5.10 (m, 1H), 4.55 (t, *J*=7.4 Hz, 1H), 3.81 (s, 3H), 3.26 - 3.20 (m, 2H), 2.54 - 2.41 (m, 2H), 2.04 - 1.85 (m, 3H), 1.84 - 1.77 (m, 1H), 1.74 - 1.62 (m, 2H), 1.56 - 1.47 (m, 1H), 0.95 - 0.79 (m, 1H), 0.60 - 0.47 (m, 2H), 0.19 (br dd, *J*=4.8, 10.0 Hz, 2H).

Example 178. Synthesis of viral protease inhibitor compound 621



Step 1: (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide

[0001435] To a solution of benzyl *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (400 mg, 0.92 mmol, 1 *eq*) in MeOH (5 mL) was added Pd (200 mg, 10% purity) and H_2 (0.92 mmol) .The mixture was stirred at 25 °C under 15psi for 1 h . LCMS showed one peak with desired MS was detected. The mixture was filtered to give the filter liquor. The mixture was concentrated under reduce pressure to give (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (274 mg, 99.5% yield) as a white solid.

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

[0001436] To a solution of (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (137 mg, 0.46 mmol, 1 *eq*) and 5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic acid (88.8 mg, 0.46 mmol, 1 *eq*) in DMF (2 mL) was added DIPEA (119.4 mg, 0.92 mmol, 0.16 mL, 2 *eq*) and HATU (210.9 mg, 0.55 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 1 h . LCMS showed one peak with desired MS was detected. The mixture was concentrated under reduce

pressure. The residue was purified by flash silica gel chromatography (ISCO®;12 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @ 30 mL/min) to give Compound *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxamide (144 mg, 63.1% yield) as a white solid.

[0001437] LCMS: Rt = 0.675 min; for $C_{23}H_{30}N_6O_5$ MS Calcd.: 470.23; MS Found: 471.1 [$M+H^+$].

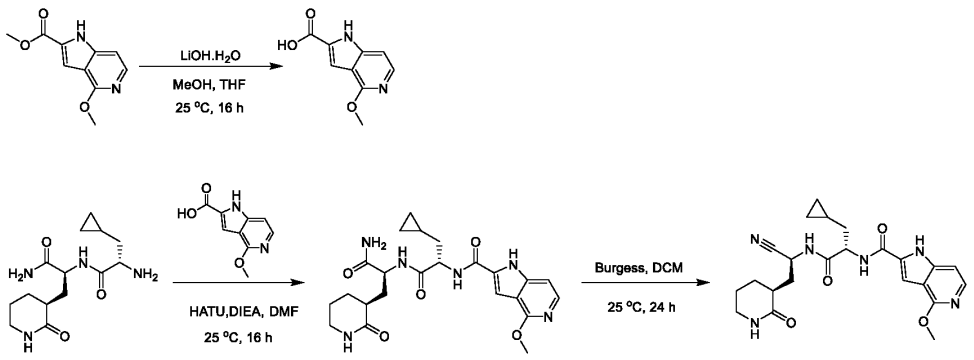
Step 3: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

[0001438] To a solution of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxamide (44 mg, 93.5 umol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (66.86 mg, 0.28 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 25 °C for 12 hr. LCMS showed one peak with desired MS was detected. The mixture was quenched with H_2O (10 mL), and extracted with DCM (20 mL * 3). The combined organic layers was washed with brine (10 mL) dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80 * 40 mm * 3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 23%-53%, 7.8 min) to give compound *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxamide (12.08 mg, 9.3% yield) as a white solid.

[0001439] LCMS: Rt = 0.727 min; for $C_{23}H_{28}N_6O_4$ MS Calcd.: 452.22; MS Found: 453.1 [$M+H^+$].

[0001440] ^{1}H NMR (400 MHz, CD_3OD) δ7.79 - 7.74 (m, 1H), 7.17 (s, 1H), 6.72 (d, *J*=9.0 Hz, 1H), 5.17 - 5.04 (m, 1H), 4.56 (t, *J*=7.4 Hz, 1H), 3.97 - 3.96 (m, 1H), 3.95 (s, 2H), 3.26 - 3.19 (m, 2H), 2.56 - 2.40 (m, 2H), 2.02 - 1.87 (m, 3H), 1.85 - 1.78 (m, 1H), 1.76 - 1.63 (m, 2H), 1.59 - 1.46 (m, 1H), 0.90 - 0.77 (m, 1H), 0.59 - 0.46 (m, 2H), 0.27 - 0.07 (m, 2H).

Example 179. Synthesis of viral protease inhibitor compound 623



Step 1: Methoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0001441] To a solution of methyl 4-methoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (150 mg, 0.72 mmol, 1 eq) in THF (1 mL) was added LiOH.H_2O (30.5 mg, 0.72 mmol, 1 eq) and MeOH (0.5 mL). The mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL *3). The aqueous layer acidified with concentrated HCl and extracted with DCM. The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with petroleum ether at 25 °C for 60 min. Compound 4-methoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid (120 mg, 84.9% yield, 99% purity) was obtained as white solid.

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0001442] A solution of (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (150 mg, 0.50 mmol, 1 eq) in DMF (1 mL) was added HATU (192.4 mg, 0.50 mmol, 1 eq), 4-methoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid (106.9 mg, 0.55 mmol, 1.1 eq) and DIEA (130.8 mg, 1.01 mmol, 0.17 mL, 2 eq) was stirred at 25 °C for 16 hr. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL *3). The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-

oxo-ethyl]-4-methoxy-1*H*-pyrrolo[3,2-c]pyridine-2-carboxamide (110 mg, crude) was obtained as white solid.

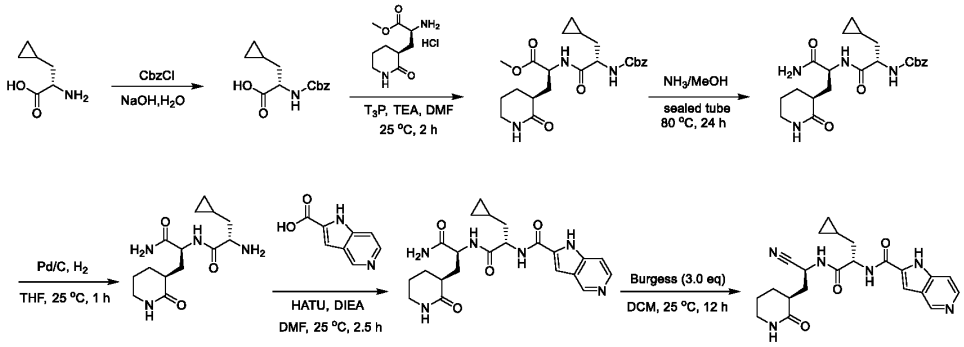
Step 3: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0001443] To a solution of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-pyrrolo[3,2-c]pyridine-2-carboxamide (110 mg, 0.23 mmol, 1 *eq*) in DCM (1 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (167.1 mg, 0.70 mmol, 3 eq). The mixture was stirred at 25 °C for 24 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL *3). The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water (0.05% NH_3H_2O + 10 mM NH_4HCO_3)-ACN];B%: 15%-45%,9.5 min). Compound *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1*H*-pyrrolo[3,2-c]pyridine-2-carboxamide (40.69 mg, 38.4% yield, 100% purity) was obtained as white solid.

[0001444] LCMS： Rt = 1.387 min; for $C_{23}H_{28}N_6O_4$ MS Calcd.: 452.51; MS Found: 453.1 [$M+H^+$].

[0001445] ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (d, *J* = 6.0 Hz, 1H), 7.34 (s, 1H), 7.05 (d, *J* = 6.3 Hz, 1H), 4.47 (dd, *J* = 4.0, 11.8 Hz, 1H), 4.57 (dd, *J* = 6.0, 8.3 Hz, 1H), 4.05 (s, 3H), 3.28 - 3.17 (m, 2H), 2.47 - 2.35 (m, 1H), 2.28 (ddd, *J* = 4.4, 12.0, 14.0 Hz, 1H), 2.08 - 1.95 (m, 1H), 1.90 - 1.77 (m, 3H), 1.77 - 1.63 (m, 2H), 1.62 - 1.48 (m, 1H), 0.96 - 0.78 (m, 1H), 0.59 - 0.42 (m, 2H), 0.26 - 0.11 (m, 2H).

Example 180. Synthesis of viral protease inhibitor compound 625



Step 1: (2S)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoic acid

[0001446] A solution of (2*S*)-2-amino-3-cyclopropyl-propanoic acid (5 g, 38.71 mmol, 1 eq) was added NaOH (1 M, 135.4 mL, 3.5 eq) and benzyl carbonochloridate (8.5 g, 50.33 mmol, 7.1 mL, 1.3 eq) was stirred at 25 °C for 2 hr. TLC (petroleum ether/ethyl acetate = 1:1, PMA). The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL *3). The aqueous layer acidified with concentrated HCl and extracted with DCM. The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound (2*S*)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoic acid (7.7 g, 68.1% yield, 90% purity) was obtained as white solid.

Step 2: (S)-methyl2-((S)-2-(((benzyloxy)carbonyl)amino)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001447] To a solution of (2S)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoic acid (3.5 g, 13.29 mmol, 1 *eq*) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (3.15 g, 13.29 mmol, 1 *eq*, HCl)in DMF (60 mL) was added TEA (4.04 g, 39.88 mmol, 5.55 mL, 3 *eq*) and T_3P (8.46 g, 13.29 mmol, 7.91 mL, 50% purity, 1 *eq*). The mixture was stirred at 25 °C for 2 hr. TLC (petroleum ether/ethyl acetate = 0:1, I_2). LCMS detected desired compound. The reaction mixture was added H_2O (10 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ether gradient @ 40 mL/min). Compound methyl(2S)-2-[[(2S)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-

piperidyl]propanoate (4.5 g, 9.49 mmol, 71.4% yield, 94% purity) was obtained as a colorless oil.

Step 3: benzyl((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate

[0001448] To a stirred solution of methyl (2S)-2-[[(2S)-2-(benzyloxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (4.5 g, 10.10 mmol, 1 *eq*) in MeOH (10 mL) was added with a solution of NH_3 (7 M, 50 mL, 34.65 *eq*). The mixture was allowed to stir at 80 °C for 24 h in a sealed tube. TLC (DCM/MeOH = 10:1, I_2). LCMS detected the desired compound. The reaction mixture concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~5% DCM/MeOH @ 40 mL/min). Compound benzyl N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (3.6 g, 7.69 mmol, 76.17% yield, 92% purity) was obtained as a white solid.

Step 4: (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-cyclopropylpropanamide

[0001449] To a solution of benzyl N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (800 mg, 1.86 mmol, 1 *eq*) in MeOH (3 mL) was added Pd/C (100 mg, 1.86 mmol, 10% purity, 1 *eq*). The mixture was stirred at 25 °C for 2 h under H_2 (15 psi). LCMS indicated starting was consumed completely and detected desired compound. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Compound (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (550 mg, 1.86 mmol, 99.87% yield) was obtained as colorless oil.

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0001450] A mixture of 1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid (90.2 mg, 0.55 mmol, 1.1 *eq*), HATU (288.6 mg, 0.75 mmol, 1.5 *eq*) and DIPEA (196.2 mg, 1.52 mmol, 0.26 mL, 3 *eq*) in DMF (2 mL) was stirred at 25 °C for 0.5 h, and then (2S)-2-amino-N-

[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (150 mg, 0.50 mmol, 1 *eq*) was added into the reaction. The resulting mixture was stirred 25 °C for 2 hr. TLC (DCM/MeOH = 5:1, UV 254) indicated starting material was consumed completely and new spots formed. LCMS detected desired compound. The reaction mixture was added H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% MeOH/ DCM @ 30 mL/min). Compound N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide (200 mg, 0.43 mmol, 86.1% yield, 96% purity) was obtained as a white solid.

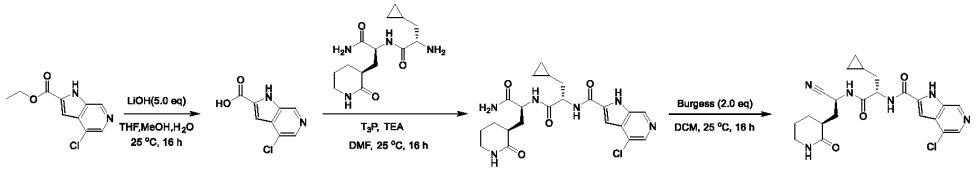
Step 6: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0001451] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide (120 mg, 0.27 mmol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (194.7 mg, 0.81 mmol, 3 *eq*). The mixture was stirred at 25 °C for 16 h under N_2. LCMS detected desired compound. The reaction mixture was added H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 7%-37%,9.5 min) to give ~20 mg crude product. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water (0.05% ammonia hydroxide v/v)-MeOH];B%: 0%-60%,7.8 min). Compound N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide (2.37 mg, 5.4 umol, 1.9% yield, 96.8% purity) was obtained as a white solid.

[0001452] LCMS: Rt = 1.321 min; for $C_{22}H_{26}N_6O_3$ MS Calcd.: 422.48; MS Found: 423.1 [$M+H^+$].

[0001453] ^{1}H NMR (400 MHz, CD_3OD) δ 9.03 (s, 1 H), 8.43 (br d, *J* = 6.27 Hz, 1 H), 8.25 (d, *J* = 6.27 Hz, 1 H), 7.14 - 7.26 (m, 1 H), 5.16 (t, *J* = 8.16 Hz, 1 H), 4.64 (br d, *J* = 2.01 Hz, 1 H), 3.25 - 3.29 (m, 2 H), 2.41 - 2.60 (m, 2 H), 1.93 - 2.09 (m, 2 H), 1.71 - 1.91 (m, 4 H), 1.49 - 1.63 (m, 1 H), 0.88 (br s, 1 H), 0.46 - 0.53 (m, 2 H), 0.12 - 0.26 (m, 2 H).

Example 181. Synthesis of viral protease inhibitor compound 669



Step 1: 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

[0001454] To a solution of ethyl 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (300 mg, 1.34 mmol, 1 *eq*) in THF (5 mL) and MeOH (2 mL) was added $LiOH.H_2O$ (280.2 mg, 6.68 mmol, 5 *eq*) and H_2O (2 mL). The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove MeOH and THF. Then the pH of the residue was adjusted (neutralized) to about 6-7 with 2 M HCl, filtered, and then the cake concentrated under reduced pressure to give a residue. 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (190 mg, 0.96 mmol, 72.3% yield) was obtained as a white solid.

Step 3: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

[0001455] To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (70 mg, 0.35 mmol, 1 *eq*) and (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (105.5 mg, 0.35 mmol, 1 *eq*) in DMF (2 mL) was added T_3P (226.5 mg, 0.35 mmol, 0.21 mL, 50% purity, 1 *eq*) and TEA (108.0 mg, 1.07 mmol, 0.14 mL, 3 *eq*). The mixture was stirred at 25 °C for 2 h. TLC (DCM/MeOH = 5:1, UV 254). The reaction mixture was added with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~15% MeOH/DCM @ 30 mL/min). Compound N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-

oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (80 mg, 0.16 mmol, 46.8% yield, 99% purity) was obtained as a white solid.

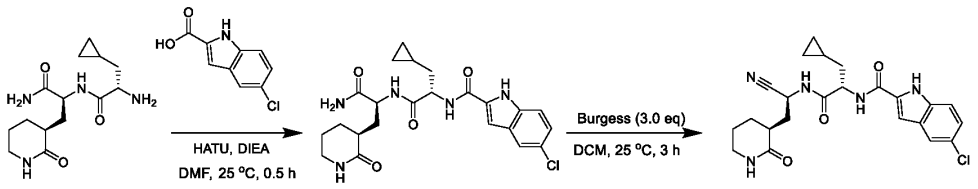
Step 3: 4-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

[0001456] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (60 mg, 0.12 mmol, 1 *eq*) in DCM (2 mL) was added Burgess (60.2 mg, 0.25 mmol, 2 *eq*). The mixture was stirred at 25 °C for 16 h under N_2. The reaction mixture was added with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5 um; mobile phase: [water (0.05% ammonia hydroxide v/v)-MeOH]; B%: 53%-83%,7.8 min). Compound 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (9.41 mg, 19.8 umol, 15.7% yield, 96.6% purity) was obtained as a white solid.

[0001457] LCMS: Rt = 1.895 min; for $C_{22}H_{25}ClN_6O_3$ MS Calcd.: 456.93; MS Found: 457.1 [$M+H^+$].

[0001458] ^1H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1 H), 8.13 (s, 1 H), 7.35 - 7.39 (m, 1 H), 5.14 (dd, *J* = 10.04, 6.02 Hz, 1 H), 4.56 (t, *J* = 7.53 Hz, 1 H), 3.22 - 3.28 (m, 2 H), 2.40 - 2.57 (m, 2 H), 1.88 - 2.05 (m, 3 H), 1.82 (td, *J* = 9.16, 4.27 Hz, 1 H), 1.68 (dd, *J* = 14.43, 7.15 Hz, 1 H), 1.47 - 1.58 (m, 1 H), 1.31 (t, *J* = 7.28 Hz, 1 H), 0.80 - 0.91 (m, 1 H), 0.48 - 0.57 (m, 2 H), 0.15 - 0.26 (m, 2 H).

Example 182. Synthesis of viral protease inhibitor compound 633



Step 1: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1H-indole-2-carboxamide

[0001459] To a solution of (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (100.0 mg, 0.33 mmol, 1 *eq*) and 5-chloro-1*H*-indole-2-carboxylic acid (66.0 mg, 0.33 mmol, 1 *eq*) in DMF (2 mL) was added HATU (153.9 mg, 0.40 mmol, 1.2 *eq*) and DIEA (87.2 mg, 0.67 mmol, 0.11 mL, 2 *eq*). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to remove DMF. The residue was diluted with H_2O (10 mL) and extracted with ethyl acetate (25 mL * 3). The combined organic layers were washed with Brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol /Dichloromethane@ 20 mL/min). Compound *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1*H*-indole-2-carboxamide (150.0 mg, 90.9% yield) was obtained as a yellow solid.

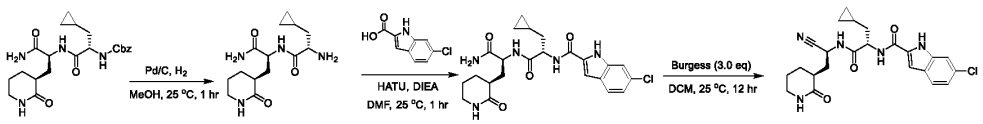
Step 2: 5-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001460] To a solution of N-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1*H*-indole-2-carboxamide (129.0 mg, 0.27 mmol, 1 *eq*) in DCM (2.5 mL) was added Burgess reagent (259.4 mg, 1.09 mmol, 4 *eq*) at 0 °C. The mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was diluted with H_2O (15 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 31%-61%, 7.8 min). Compound 5-chloro-*N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1*H*-indole-2-carboxamide (40.2 mg, 30.2% yield) was obtained as a white solid.

[0001461] LCMS: Rt = 0.832 min; for $C_{23}H_{26}ClN_5O_3$ MS Calcd.: 455.94; MS Found: 456.1 [$M+H^+$].

[0001462] ^1H NMR (400 MHz, CD_3OD) δ 7.61 (d, *J*=1.8 Hz, 1H), 7.41 (d, *J*=8.8 Hz, 1H), 7.19 (dd, *J*=2.0, 8.8 Hz, 1H), 7.14 (s, 1H), 5.13 (br dd, *J*=6.1, 10.2 Hz, 1H), 4.57 - 4.52 (m, 1H), 3.24 - 3.20 (m, 1H), 2.56 - 2.40 (m, 2H), 2.05 - 1.84 (m, 4H), 1.80 - 1.59 (m, 3H), 1.57 - 1.42 (m, 1H), 0.85 (br s, 1H), 0.54 (br d, *J*=8.3 Hz, 2H), 0.19 (br dd, *J*=5.1, 9.9 Hz, 2H).

Example 183. Synthesis of viral protease inhibitor compound 635



Step 1: (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide

[0001463] To a solution of benzyl *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (400 mg, 0.92 mmol, 1 *eq*) in MeOH (5 mL) was added Pd (200 mg, 10% purity) and H_2 (0.92 mmol). The mixture was stirred at 25 °C under 15 psi for 1 h . The mixture was filtered to give the filter liquor and the reaction was concentrated under reduce pressure to give (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (274 mg, 0.92 mmol, 99.5% yield) as a white solid.

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-1H-indole-2-carboxamide

[0001464] To a solution of (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (137 mg, 0.46 mmol, 1 *eq*) and 6-chloro-1*H*-indole-2-carboxylic acid (90.4 mg, 0.46 mmol, 1 *eq*) in DMF (2 mL) was added DIPEA (119.4 mg, 0.92 mmol, 0.16 mL, 2 *eq*) and HATU (210.9 mg, 0.55 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduce pressure, and the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @ 30 mL/min) to give *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-

piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-1*H*-indole-2-carboxamide (200 mg, 89.0% yield) as a white solid.

[0001465] LCMS: Rt = 0.780 min; for $C_{23}H_{28}ClN_5O_4$ MS Calcd.: 473.18; MS Found: 474.1 [$M+H^+$].

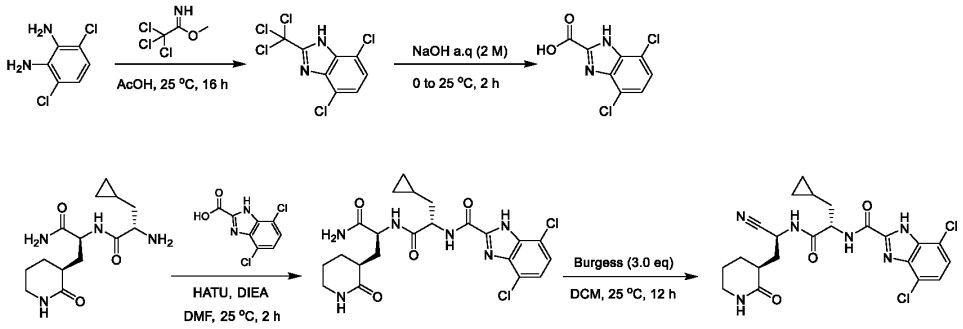
Step 3: 6-Chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001466] To a solution of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-1*H*-indole-2-carboxamide (47.5 mg, 0.1 mmol, 1 *eq*) in DCM (1 mL) was added Burgess reagent (71.6 mg, 0.3 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 25 °C for 12 h. The mixture was concentrated under reduce pressure, and the residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80 * 40 mm * 3 um; mobile phase: [water(0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN];B%: 31%-61%,7.8 min) to give 6-chloro-*N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1*H*-indole-2-carboxamide(64.33 mg, 34.7% yield) as a white solid.

[0001467] LCMS: Rt = 0.832 min; for $C_{23}H_{26}ClN_5O_3$; MS Calcd.:455.17; MS Found: 456.1 [$M+H^+$].

[0001468] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (br s, 1H), 8.95 (br d, *J*=8.0 Hz, 1H), 8.66 (br d, *J*=7.5 Hz, 1H), 7.66 (d, *J*=8.5 Hz, 1H), 7.53 (br s, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 7.05 (dd, *J*=1.8, 8.5 Hz, 1H), 5.11 - 4.96 (m, 1H), 4.52 - 4.42 (m, 1H), 3.09 (br s, 2H), 2.34 - 2.21 (m, 2H), 1.89 - 1.75 (m, 3H), 1.74 - 1.65 (m, 1H), 1.56 (br s, 1H), 1.51 - 1.29 (m, 2H), 0.79 (br s, 1H), 0.42 (br d, *J*=7.0 Hz, 2H), 0.23 - 0.01 (m, 2H).

Example 184. Synthesis of viral protease inhibitor compound 637



Step 1: 4,7-Dichloro-2-(trichloromethyl)-1H-benzimidazole

[0001469] To a solution of 3,6-dichlorobenzene-1,2-diamine (0.3 g, 1.69 mmol, 1 eq) in AcOH (12.57 g, 209.2 mmol, 11.97 mL, 123.8 eq) was added methyl 2,2,2-trichloroacetimidate (313.0 mg, 1.77 mmol, 0.21 mL, 1.05 eq) at 0 °C. The mixture was stirred at 25 °C for 16 h. LC-MS showed 48% of 1 was remained and 43% of desired compound was detected. The reaction mixture was diluted with H_2O (40 mL) and filtered to give 2 (300 mg, crude) as a white solid.

Step 2: 4,7-Dichloro-1H-benzimidazole-2-carboxylic acid

[0001470] To a solution of NaOH (0.8 g, 20.0 mmol, 20.2 eq) in H_2O (10 mL) was added 4,7-dichloro-2-(trichloromethyl)-1H-benzo[d]imidazole (0.3 g, 985.58 umol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h. The pH of the mixture was adjusted with HCl (2 M) to 2-3 and then the mixture was filtered to give 4,7-dichloro-1H-benzo[d]imidazole-2-carboxylic acid (0.2 g, crude) as a white solid.

Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,6-dichloro-1H-benzimidazole-2-carboxamide

[0001471] To a solution of (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-cyclopropylpropanamide (130 mg, 0.43 mmol, 1 eq) and 4,7-dichloro-1H-benzo[d]imidazole-2-carboxylic acid (101.3 mg, 0.43 mmol, 1.0 eq) in DMF (3 mL) was added HATU (250.1 mg, 0.65 mmol, 1.5 eq) and DIPEA (113.3 mg, 0.87 mmol, 0.15 mL, 2.0 eq). The mixture was stirred at 25 °C for 1 h. TLC (Dichloromethane: Methanol=10/1, UV). The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=100/1 to 10/1) to give N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-

oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,7-dichloro-1H-benzo[d]imidazole-2-carboxamide (0.2 g, 0.39 mmol, 89% yield) as a white solid.

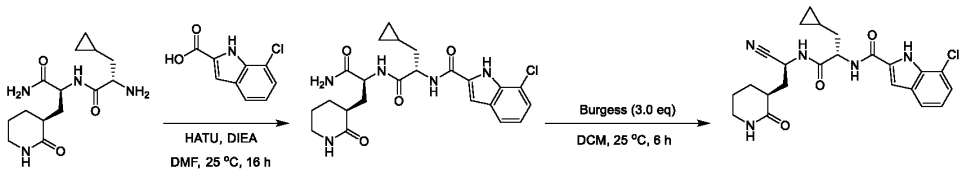
Step 4: 4,7-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-benzimidazole-2-carboxamide

[0001472] To a solution of N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,7-dichloro-1H-benzo[d]imidazole-2-carboxamide (100.00 mg, 0.19 mmol, 1 eq) in DCM (3.0 mL) was added Burgess reagent (140.3 mg, 0.58 mmol, 3.0 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH4HCO3)-ACN]; B%: 20%-50%, 7.8 min) to give compound 637 (22.11 mg, 22% yield) as a white solid.

[0001473] LCMS: Rt = 0.824 min; for $C_{22}H_{24}Cl_2N_6O_3$ MS Calcd.: 490.13; MS Found: 491.1 [$M+H^+$].

[0001474] ^1H NMR (400 MHz, CD_3OD) δ 7.30 (s, 2H), 5.22 - 5.09 (m, 1H), 4.60 (t, *J* = 7.1 Hz, 1H), 3.27 - 3.19 (m, 2H), 2.56 - 2.37 (m, 2H), 2.06 - 1.88 (m, 3H), 1.87 - 1.79 (m, 1H), 1.73 (td, *J* = 7.2, 14.0 Hz, 2H), 1.60 - 1.44 (m, 1H), 0.96 - 0.75 (m, 1H), 0.54 (d, *J* = 6.9 Hz, 2H), 0.21 (dd, *J* = 4.8, 10.4 Hz, 2H).

Example 185. Synthesis of viral protease inhibitor compound 639



Step 1: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide

[0001475] To a solution of (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (70 mg, 0.23 mmol, 1 eq) in DMF (1 mL) was added HATU (89.8 mg, 0.23 mmol, 1 eq), 7-chloro-1H-indole-2-carboxylic acid (50.8 mg, 0.25 mmol, 1.1 eq) and DIEA (61.0 mg, 0.47 mmol, 82.2 uL, 2 eq). The

mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL *3). The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water(0.05% NH_3H_2O + 10 mM NH_4HCO_3)-ACN];B%: 16%-46%,9.5 min). Compound *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1*H*-indole-2-carboxamide (67 mg, 0.12 mmol, 53.8% yield, 90% purity) was obtained as a white solid.

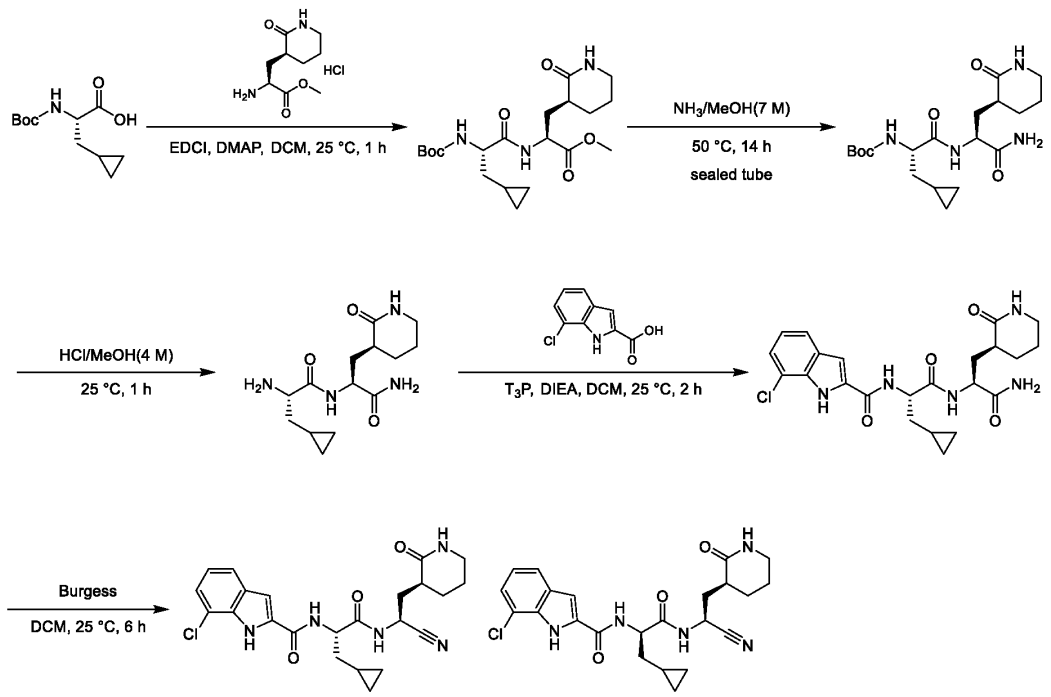
Step 2: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001476] To a solution of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1*H*-indole-2-carboxamide (60 mg, 0.12 mmol, 1 eq) in DCM (1 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (90.5 mg, 0.37 mmol, 3 eq). The mixture was stirred at 25 °C for 6 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL *3). The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water(0.05% NH_3H_2O + 10 mM NH_4HCO_3)-ACN];B%: 26%-56%,7.8 min). 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (12.34 mg, 21.3% yield, 100% purity) was obtained as white solid.

[0001477] LCMS： Rt = 2.130 min; for $C_{23}H_{26}ClN_5O_3$ MS Calcd.: 455.94; MS Found: 456.1 [$M+H^+$].

[0001478] ^1H NMR (400 MHz, CD_3OD) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.32 - 7.21 (m, 2H), 7.07 (t, *J* = 7.8 Hz, 1H), 5.14 (dd, *J* = 6.0, 10.0 Hz, 1H), 4.57 (t, *J* = 7.4 Hz, 1H), 3.28 - 3.16 (m, 2H), 2.56 - 2.28 (m, 2H), 2.05 - 1.88 (m, 3H), 1.87 - 1.78 (m, 1H), 1.77 - 1.61 (m, 2H), 1.59 - 1.44 (m, 1H), 0.92 - 0.80 (m, 1H), 0.60 - 0.49 (m, 2H), 0.26 - 0.14 (m, 2H).

Example 185a. Synthesis of viral protease inhibitor compound 639 & 639A



Step 1: Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001479] To a solution of (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (1.07 g, 4.65 mmol, 1.1 eq), methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 4.22 mmol, 1 eq, HCl) in DCM (10 mL) was added the DMAP (1.55 g, 12.67 mmol, 3 eq), EDCI (1.62 g, 8.45 mmol, 2 eq), and the resulting solution was stirred at 25 °C for 1 h. Upon completion, the solution was diluted with H_2O (30 mL), extracted with ethyl acetate (30 mL * 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 30/1 to 10/1) to give methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl] propanoate (1.2 g, 2.92 mmol, 68.97% yield, 100% purity) as a yellow oil. MS (ESI) *m/z* 412.3 $[M+H]^+$.

Step 2: (2R)-N-(4-(tert-butyl)phenyl)-N-(2-oxo-1-(pyridin-3-yl)-2-((pyridin-4-ylmethyl)amino)ethyl)pyrrolidine-2-carboxamide

[0001480] Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (600 mg, 1.46 mmol, 1 eq) in ammonia (7 M, 7.2 mL, 8.30 eq) was stirred at 50 °C for 14 h. Upon completion, the solution was concentrated to give Tert-butyl N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl] methyl] ethyl] amino]-1-(cyclopropylmethyl)-2-oxo-ethyl] carbamate (580 mg, crude) as a yellow oil. MS (ESI) *m/z* 397.3 $[M+H]^+$.

Step 3: (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide

[0001481] A solution of tert-butyl N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (580 mg, 1.46 mmol, 1 eq) in HCl/MeOH (4 M, 10.00 mL, 7.93 eq) was stirred at 25 °C for 1 h. Upon completion, the solution was concentrated to give (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (380 mg, crude) was obtained as a yellow oil. MS (ESI) *m/z* 297.2 $[M+H]^+$.

Step 4: (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide

[0001482] To a solution of (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (380 mg, 1.28 mmol, 1 eq) in DCM (3 mL) was added 7-chloro-1H-indole-2-carboxylic acid (275.88 mg, 1.41 mmol, 1.1 eq), T3P (1.22 g, 1.93 mmol, 1.14 mL, 50% purity, 1.5 eq) and DIEA (331.44 mg, 2.56 mmol, 446.68 uL, 2 eq) The mixture was stirred at 25 °C for 2 h. Upon completion, the solution was diluted with H_2O (20 mL), extracted with DCM (30 mL * 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated to give the crude. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (350 mg, 738.47 umol, 57.59% yield, 100% purity) as yellow oil. MS (ESI) *m/z* 474.3 $[M+H]^+$.

Step 5: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001483] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-

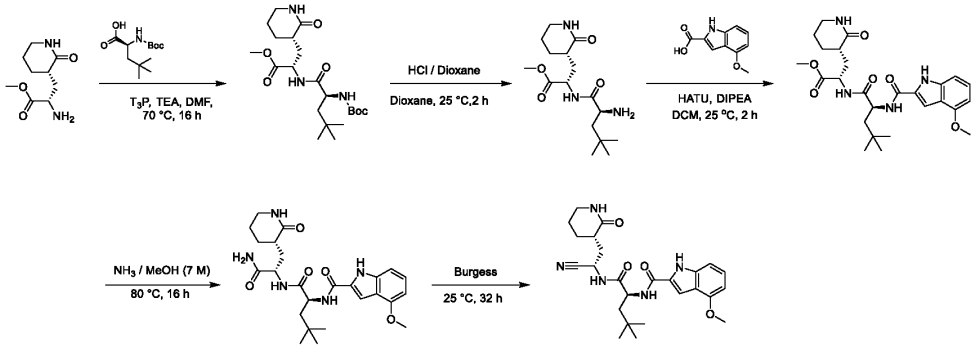
2-carboxamide (350 mg, 738.47 umol, 1 eq) in DCM (4 mL) was added Burgess reagent (527.94 mg, 2.22 mmol, 3 eq), and the solution was stirred at 25 °C for 6 h. Upon completion, DCM was removed using blow dry to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; mobile phase: [water(0.05% NH_3H_2O+10 mM $NH4HCO_3$)-ACN];B%: 25%-55%,8 min) to give desired compound as a white solid, which was further separated by SFC (column: DAICEL CHIRALPAK AS(250 mm*30 mm, 10 um);mobile phase: [0.1% NH_3H_2O ETOH];B%: 33%-33%,8 min) to give 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (250 mg, 530.89 umol, 74.25% yield, 96.82% purity) as a white solid. MS (ESI) *m/z* 456.2 $[M+H]^+$.

[0001484] ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.58 (d, *J*=7.9 Hz, 1H), 7.35 - 7.20 (m, 2H), 7.06 (t, *J*=7.8 Hz, 1H), 5.22 - 5.05 (m, 1H), 4.57 (t, *J*=7.5 Hz, 1H), 3.27 - 3.14 (m, 2H), 2.61 - 2.34 (m, 2H), 2.09 - 1.61 (m, 6H), 1.59 - 1.43 (m, 1H), 0.98 - 0.76 (m, 1H), 0.55 (dd, *J*=1.3, 8.2 Hz, 2H), 0.31 - 0.09 (m, 2H).

[0001485] 7-Chloro-N-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (45 mg, 98.70 umol, 13.37% yield, 100% purity) was obtained as white solid. MS (ESI) *m/z* 456.2 $[M+H]^+$.

[0001486] ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.59 (dd, *J*=0.9, 7.9 Hz, 1H), 7.32 - 7.21 (m, 2H), 7.07 (t, J=7.8 Hz, 1H), 5.12 - 5.02 (m, 1H), 4.59 (dd, *J*=6.4, 7.9 Hz, 1H), 3.21 (dd, *J*=4.6, 7.7 Hz, 2H), 2.44 - 2.23 (m, 2H), 2.09 - 1.62 (m, 6H), 1.60 - 1.47 (m, 1H), 0.94 - 0.78 (m, 1H), 0.62 - 0.43 (m, 2H), 0.27 - 0.11 (m, 2H).

Example 186. Synthesis of viral protease inhibitor compound 643



Step 1: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001487] T_3P (2.69 g, 4.22 mmol, 2.51 mL, 50% purity, 2 *eq*) was added to a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 2.11 mmol, 1 *eq*, HCl), (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (570.0 mg, 2.32 mmol, 1.1 *eq*) and TEA (855.0 mg, 8.45 mmol, 1.18 mL, 4 *eq*) in DMF (5 mL). Then the mixture was stirred at 70 °C for 16 h. TLC (petroleum ether:ethyl acetate = 0:1/PMA). The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®;20 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ether gradient @30 mL/min). Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (436 mg, 0.99 mmol, 47.2% yield, 97.9% purity) was obtained as white solid and confirmed by LC-MS, SFC and HNMR.

Step 2: methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001488] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (300 mg, 0.70 mmol, 1 *eq*) in HCl/dioxane (4 M, 175.42 uL, 1 *eq*) was stirred at 25 °C for 2 h. The reaction mixture was filtered to afford ethyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (250 mg, crude, HCl) as a white solid.

Step 3: methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001489] A mixture of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (310 mg, 0.85 mmol, 1 *eq*, HCl), 4-methoxy-1H-indole-2-carboxylic acid (179.1 mg, 0.93 mmol, 1.1 *eq*), HATU (647.8 mg, 1.70 mmol, 2 *eq*) and DIPEA (440.4 mg, 3.41 mmol, 0.60 mL, 4 *eq*) in DCM (4 mL) was stirred at 25 °C for 2 h. TLC (PE:EA=0:1/UV254nm). The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ether gradient @ 30mL/min). Methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (451 mg, 0.68 mmol, 80.1% yield, 75.8% purity) was obtained as a yellow oil.

Step 4: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[0001490] To a mixture of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (400 mg, 0.79 mmol, 1 *eq*) was added NH_3 (7 M, 11.42 mL, 100 *eq*), and then the resulting mixture was stirred at 80 °C for 16 h. TLC (DCM:MeOH=10:1/UV254nm). The reaction mixture was concentrated in vacuum, and the residue was purified by flash silica gel chromatography (ISCO®;12g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/MeOH@30 mL/min). N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (295 mg, 0.60 mmol, 75.1% yield, 98.9% purity) was obtained as white a solid.

Step 5: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide

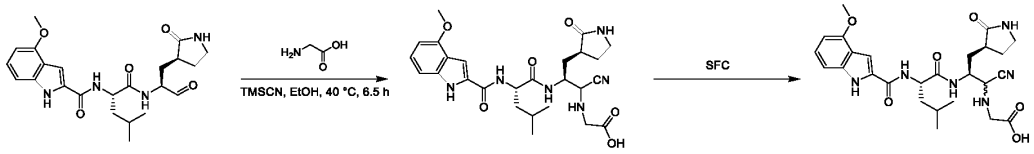
[0001491] Methoxycarbonyl-(triethylammonio)sulfonyl-azanide (284.6 mg, 1.19 mmol, 2 *eq*) was added to a mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (290 mg, 0.59 mmol, 1 *eq*) in DCM (3 mL) at 25 °C. Then the mixture was

stirred at 25 °C for 16 h. Then, methoxycarbonyl-(triethylammonio)sulfonyl-azanide (142.3 mg, 0.59 mmol, 1 *eq*) was added to the mixture and the mixture was stirred at 25 °C for another 16 h. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5 um; mobile phase: [water (0.05% ammonia hydroxide v/v)-MeOH];B%: 55%-85%, 9.5 min). N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (28.1 mg, 59.3 umol, 9.9% yield, 98.7% purity) was obtained as a white solid.

[0001492] LCMS: Rt = 0.832 min; for $C_{25}H_{33}N_5O_4$ MS Calcd.: 467.25, MS Found: 468.2 [$M+H^+$].

[0001493] ^1H NMR (400 MHz, CD_3OD) δ 7.26 - 7.22 (m, 1H), 7.18 - 7.12 (m, 1H), 7.05 - 7.00 (m, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 5.08 (dd, *J* = 6.3, 9.8 Hz, 1H), 4.67 - 4.63 (m, 1H), 3.93 (s, 3H), 3.21 - 3.15 (m, 2H), 2.47 - 2.38 (m, 2H), 1.98 - 1.72 (m, 6H), 1.70 - 1.58 (m, 1H), 1.54 - 1.43 (m, 1H), 1.02 (s, 8H), 1.04 - 1.01 (m, 2H).

Example 187. Synthesis of viral protease inhibitor compound 653



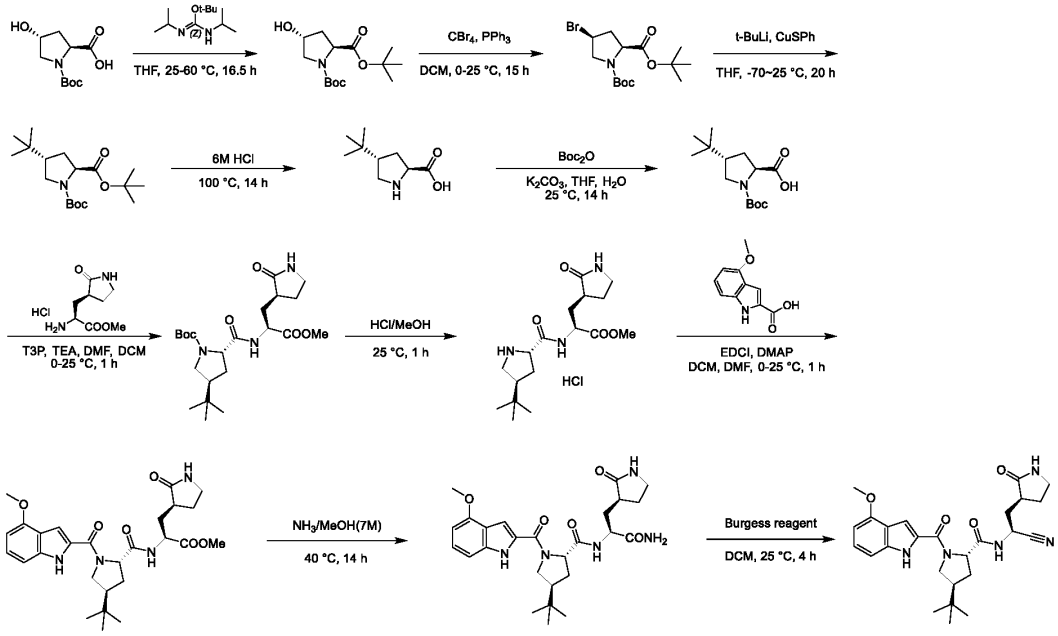
[0001494] To a mixture of N-[(1S)-1-[[(1S)-1-formyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3-methyl -butyl]-4-methoxy-1H-indole-2-carboxamide (1 g, 1.81 mmol, 80% purity, 1 eq) in EtOH (20 mL) was added 2-aminoacetic acid (271.74 mg, 3.62 mmol, 20.52 uL, 2 eq), $ZnCl_2$ (1 M, 18.10 uL, 0.01 eq). The mixture was stirred at 25 °C for 30 min, and then added TMSCN (359.14 mg, 3.62 mmol, 452.89 uL, 2 eq). The mixture was stirred at 40 °C for 6 h. Upon the reaction was completed, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by HCl prep-HPLC (column: Phenomenex luna C18 80*40 mm*3 um; mobile phase: [water (0.04%HCl)-ACN]; B%: 25%-45%, 7 min) to get a mixture.

The mixture was separated by SFC (column: DAICEL CHIRALPAK AD (250 mm*30 mm, 10 um); mobile phase: [Neu-ETOH]; B%: 50%-50%, 10 min) to get the compound 2-[[(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino] -3-[(3S)-2-oxopyrrolidin-3-yl]propyl]amino]acetic acid (125 mg, 235.87 umol, 13.03% yield, 99.363% purity) and 2-[[(2S)-1-cyano-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl -pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propyl]amino]acetic acid (205 mg, 373.82 umol, 20.65% yield, 96.023% purity) as white solid. MS (ESI) *m/z* 527.3 $[M+H]^+$.

[0001495] Isomer 1: ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.56 (d, *J*=2.0 Hz, 1H), 8.52 - 8.21 (m, 2H), 7.58 (s, 1H), 7.35 (d, *J*=1.7 Hz, 1H), 7.14 - 7.05 (m, 1H), 7.03 - 6.97 (m, 1H), 6.50 (d, *J*=7.7 Hz, 1H), 4.57 - 4.41 (m, 1H), 4.14 (tdd, *J*=4.2, 8.2, 12.2 Hz, 1H), 3.97 - 3.82 (m, 4H), 3.52 - 3.36 (m, 2H), 3.18 - 2.98 (m, 2H), 2.41 - 2.27 (m, 1H), 2.12 - 2.04 (m, 2H), 1.82 - 1.36 (m, 5H), 0.91 (dd, *J*=6.4, 15.8 Hz, 6H)

[0001496] Isomer 2: ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.57 (d, *J*=2.0 Hz, 1H), 8.39 (d, *J*=7.8 Hz, 1H), 8.20 (d, *J*=9.5 Hz, 1H), 7.54 (s, 1H), 7.37 (d, *J*=1.6 Hz, 1H), 7.16 - 6.94 (m, 2H), 6.50 (d, *J*=7.6 Hz, 1H), 4.53 - 4.36 (m, 1H), 4.18 - 4.01 (m, 1H), 3.88 (s, 3H), 3.77 (d, *J*=8.8 Hz, 1H), 3.43 - 3.33 (m, 2H), 3.15 - 2.96 (m, 2H), 2.38 - 2.25 (m, 1H), 2.08 - 2.01 (m, 1H), 1.91 - 1.47 (m, 6H), 0.91 (dd, *J*=6.4, 14.8 Hz, 6H).

Example 188. Synthesis of viral protease inhibitor compound 655



Step 1: (2S,4R)-di-tert-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate

[0001497] A solution of (2S,4R)-1-tert-butoxycarbonyl-4-hydroxy-pyrrolidine-2-carboxylic acid (5 g, 21.62 mmol, 1 *eq*) in THF (75 mL) was added 2-tert-butyl-1,3-diisopropyl-isourea (6.50 g, 32.43 mmol, 1.5 *eq*) at 25 °C, and then the solution was stirred at 60 °C for 2.5 h. Additional 2-tert-butyl-1,3-diisopropyl-isourea (6.50 g, 32.43 mmol, 1.5 eq) was added to the mixture and then was stirred at 60 °C for 14 h. Upon completion, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give (2S,4R)-di-tert-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate (4.3 g, 14.22 mmol, 65.75% yield, 95% purity) as colorless oil. MS (ESI) *m/z* 288.2 $[M+H]^+$

Step 2: (2S,4S)-di-tert-butyl 4-bromopyrrolidine-1,2-dicarboxylate

[0001498] A solution of (2S,4R)-di-tert-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate (4 g, 13.92 mmol, 1 *eq*) in DCM (40 mL) was added CBr_4 (14.08 g, 42.46 mmol, 3.05 *eq*) at 25 °C. The mixture was cooled to 0 °C, and PPh_3 (11.32 g, 43.15 mmol, 3.1 *eq*) was added carefully. The reaction was stirred at 25 °C for 15 h. Upon completion, ethanol (4 mL) was added, and the solution was stirred for 2 h. MTBE (40 mL) was added dropwise to precipitate the phosphine oxide, which was filtered off, and the filter cake was washed

with DCM (30 mL* 2). The filtrate was concentrated under reduced pressure to give a brown oil. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 100:0 to 10:1) to give (2S,4S)-di-tert-butyl 4-bromopyrrolidine-1,2-dicarboxylate (1.5 g, 4.07 mmol, 29.23% yield, 95% purity) as a light yellow oil.

Step 3: (2S,4S)-di-tert-butyl 4-(tert-butyl)pyrrolidine-1,2-dicarboxylate

[0001499] A mixture of phenylsulfanylcopper (1.58 g, 9.14 mmol, 6.4 *eq*) in dry THF (30 mL) was cooled to -70 °C and treated with careful addition of t-BuLi (1.3 M, 7.03 mL, 6.4 *eq*). This yellow mixture was stirred for 30 min, and a precooled (-20 °C) solution of (2S,4S)-di-tert-butyl 4-bromopyrrolidine-1,2-dicarboxylate (500 mg, 1.43 mmol, 1 *eq*) in dry THF (5 mL) was added. The reaction was stirred at -70 °C for 5 h, and then warmed to 25 °C for 15 h under N_2. Upon completion, the reaction was quenched by pouring into a solution of saturated aqueous NH_4Cl (30 mL). The aqueous mixture was stirred vigorously for 30 min. Solids were filtered off, and the phases were separated. The aqueous phase was extracted with MTBE (10 mL* 3), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated under reduced pressure to give a crude. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 100:0 to 10:1) to give (2S,4S)-di-tert-butyl 4-(tert-butyl)pyrrolidine-1,2-dicarboxylate (290 mg, 797.05 umol, 55.83% yield, 90% purity) as an off-white solid.

Step 4: (2S,4S)-4-(tert-butyl)pyrrolidine-2-carboxylic acid

[0001500] A mixture of (2S,4S)-di-tert-butyl 4-(tert-butyl)pyrrolidine-1,2-dicarboxylate (250 mg, 763.46 umol, 1 *eq*) in HCl (6 M, 2.5 mL, 19.65 *eq*) was stirred at 100 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S,4S)-4-tert-butylpyrrolidine-2-carboxylic acid (158 mg, crude, HCl) as a yellow solid.

Step 5: (2S,4S)-1-(tert-butoxycarbonyl)-4-(tert-butyl)pyrrolidine-2-carboxylic acid

[0001501] A mixture of (2S,4S)-4-tert-butylpyrrolidine-2-carboxylic acid (158 mg, 760.72 umol, 1 *eq*, HCl) in THF (1 mL) and H_2O (1 mL) was added K_2CO_3 (315.41 mg, 2.28 mmol, 3 *eq*) and Boc_2O (199.23 mg, 912.87 umol, 209.72 uL, 1.2 *eq*). The reaction was stirred at 25 °C for 14 h under N_2. Upon completion, the reaction mixture was

concentrated under reduced pressure to give (2S,4S)-1-(tert-butoxycarbonyl)-4-(tert-butyl)pyrrolidine-2-carboxylic acid (650 mg, crude) as a yellow solid.

Step 6: (2S,4S)-tert-butyl 4-(tert-butyl)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate

[0001502] To a solution of (2S,4S)-1-(tert-butoxycarbonyl)-4-(tert-butyl)pyrrolidine-2-carboxylic acid (630 mg, 696.51 umol, 30% purity, 1 *eq*) in DCM (6 mL) and DMF (3 mL) was added TEA (422.88 mg, 4.18 mmol, 581.68 uL, 6 *eq*), methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (186.11 mg, 835.82 umol, 1.2 *eq*, HCl). After adding T3P (1.33 g, 2.09 mmol, 1.24 mL, 50% purity, 3 *eq*) at 0 °C, the mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was quenched with water (10.0 mL) and extracted with DCM (10 mL * 3). The organic layers were washed with brine (10.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 10:1 to 0:1) to give *tert-butyl (2S,4S)-tert-butyl 4-(tert-butyl)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate* (240 mg, 546.02 umol, 78.39% yield) as a yellow solid. MS (ESI) *m/z* 440.3 $[M+H]^+$.

Step 7: (S)-methyl 2-((2S,4S)-4-(tert-butyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001503] A solution of tert-butyl (2S,4S)-tert-butyl 4-(tert-butyl)-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (230 mg, 523.27 umol, 1 eq) in HCl/MeOH (4 M, 2.3 mL, 17.58 eq) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (S)-methyl 2-((2S,4S)-4-(tert-butyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (196 mg, crude, HCl) as a light yellow solid. MS (ESI) m/z 340.2 $[M+H]^+$.

Step 8: (S)-methyl 2-((2S,4S)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001504] To a solution of (S)-methyl 2-((2S,4S)-4-(tert-butyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (196 mg, 521.43 umol, 1 *eq*, HCl) in DCM (2 mL) and DMF (1 mL) was added 4-methoxy-1H-indole-2-carboxylic acid

(99.69 mg, 521.43 umol, 1 *eq*), DMAP (127.41 mg, 1.04 mmol, 2 *eq*), and then EDCI (199.92 mg, 1.04 mmol, 2 *eq*) at 0 °C. The mixture was then stirred at 25 °C for 1 h. Upon completion, the mixture was quenched with water (10.0 mL) and extracted with DCM (10 mL * 3). The organic layers were washed with brine (10.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, dichloromethane: methanol = 10:1 to 4:1) to give (S)-methyl 2-((2S,4S)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (250 mg, 414.56 umol, 79.50% yield, 85% purity) as a yellow solid. MS (ESI) *m/z* 513.3 $[M+H]^+$.

Step 9: (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[0001505] A solution of (S)-methyl 2-((2S,4S)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (235 mg, 389.68 umol, 85% purity, 1 *eq*) in NH_3/MeOH (7 M, 5 mL) was stirred at 40 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (193 mg, crude) as a yellow solid. MS (ESI) *m/z* 498.3 $[M+H]^+$.

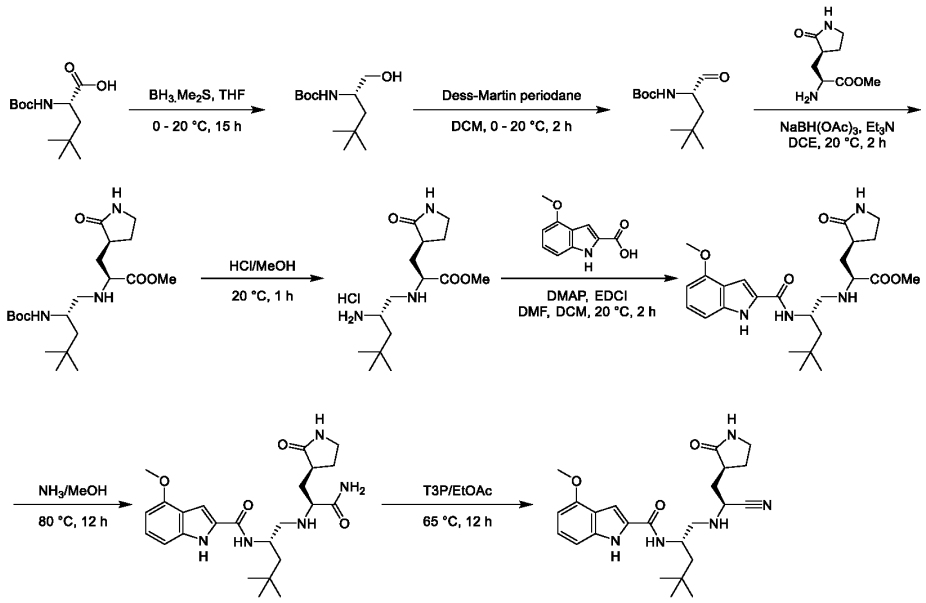
Step 10: (2S,4S)-4-(tert-butyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[0001506] To a solution of (2S,4S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-4-(tert-butyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (193 mg, 329.69 umol, 85% purity, 1 *eq*) in DCM (3 mL) was added Burgess reagent (235.71 mg, 989.08 umol, 3 *eq*), and then the reaction was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 30%-55%,10 min) to give (2S,4S)-4-(tert-butyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (59.58 mg, 124.24 umol, 37.68% yield, 100% purity) as a white solid. MS (ESI) *m/z* 480.2 $[M+H]^+$.

[0001507] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.69 - 11.55 (m, 1H), 9.17 - 8.75 (m, 1H), 7.81 - 7.44 (m, 1H), 7.16 - 7.07 (m, 1H), 7.06 - 6.98 (m, 2H), 6.55 - 6.46 (m, 1H), 5.03 - 4.53 (m, 2H), 4.04 - 3.74 (m, 4H), 3.69 - 3.36 (m, 1H), 3.22 - 2.55 (m, 2H), 2.35 - 1.95 (m, 5H), 1.83 - 1.51 (m, 3H), 1.00 - 0.82 (m, 9H).

[0001508] ^{1}H NMR (400MHz, DMSO-d$_6$, 273+80K) δ = 11.31 (s, 1H), 8.68 (s, 1H), 7.38 (s, 1H), 7.18 - 7.02 (m, 2H), 6.90 (s, 1H), 6.60 - 6.47 (m, 1H), 4.96 (q, *J*=7.6 Hz, 1H), 4.72 (s, 1H), 4.07 - 3.80 (m, 4H), 3.66 - 3.50 (m, 1H), 3.28 - 3.05 (m, 2H), 2.32 - 1.97 (m, 5H), 1.95 - 1.64 (m, 3H), 0.95 (s, 9H).

Example 189. Synthesis of viral protease inhibitor compound 659



Step 1: (S)-tert-butyl (1-hydroxy-4,4-dimethylpentan-2-yl)carbamate

[0001509] To a solution of (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (5 g, 20.38 mmol, 1 eq) in THF (100 mL) at 0 °C was added BH_3-Me_2S (10 M, 4.08 mL, 2.0 eq) drop-wise slowly, and then the mixture was stirred at 20 °C for 15 h. The reaction mixture was added into MeOH (40 mL) and stirred for 20 min. After concentrating the mixture, the residue was diluted with aq. $NaHCO_3$ (150 mL) and extracted with DCM (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 1:0 to 1:1)

to afford tert-butyl N-[(1S)-1-(hydroxymethyl)-3,3-dimethyl-butyl]carbamate (2.5 g, 10.81 mmol, 53.02% yield) as a colorless oil.

Step 2: (S)-tert-butyl (4,4-dimethyl-1-oxopentan-2-yl)carbamate

[0001510] To a solution of tert-butyl N-[(1S)-1-(hydroxymethyl)-3,3-dimethyl-butyl]carbamate (2.4 g, 10.37 mmol, 1 eq) in DCM (40 mL) was added Dess-Martin periodinane (5.72 g, 13.49 mmol, 4.18 mL, 1.3 eq) at 0 °C stirred for 1 h, and then the mixture was warm to 20 °C and stirred for 1 h. The reaction mixture was quenched by addition H_2O 60 mL at 0 °C, and then aq. $NaHCO_3$ was added drop-wise to adjust the pH of the mixture to about 8 at 0 °C and extracted with EtOAc (40 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1 to 1:1) to afford *tert*-butyl N-[(1S)-1-formyl-3,3-dimethyl-butyl]carbamate (1.6 g, 6.98 mmol, 67.25% yield) as a colorless oil.

[0001511] ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.40 (s, 1 H) 7.30 (br d, *J*=8.00 Hz, 1 H) 3.91 - 3.82 (m, 1 H) 1.66 (dd, *J*=14.38, 2.75 Hz, 1 H) 1.39 (s, 9 H) 1.32 (br d, *J*=9.26 Hz, 1 H) 0.90 (s, 9 H).

Step 3: (S)-methyl2-(((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001512] To a solution of *tert*-butyl N-[(1S)-1-formyl-3,3-dimethyl-butyl]carbamate (0.8 g, 3.49 mmol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.17 g, 5.23 mmol, 1.5 eq, HCl) in DCE (20 mL) was added Et_3N (529.52 mg, 5.23 mmol, 728.36 uL, 1.5 eq) and $NaBH(OAc)_3$ (2.22 g, 10.47 mmol, 3 eq). The reaction was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition aq. $NaHCO_3$ (100 mL) at 0 °C and stirred for 0.5 h, and then extracted with DCM (60 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 0:1 to 1:3) to afford methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (450 mg, 1.13 mmol, 32.29% yield) as a white solid. MS (ESI) *m/z* 400.3 $[M+H]^+$

Step 4: (S)-methyl 2-(((S)-2-amino-4,4-dimethylpentyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001513] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (200 mg, 500.60 umol, 1 eq) in HCl/MeOH (4 M, 4.00 mL, 31.96 eq) was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (168 mg, crude, HCl) as a white solid.

Step 5: (S)-methyl 2-(((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001514] To a solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (168 mg, 500.20 umol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (95.63 mg, 500.20 umol, 1 eq) in DMF (1 mL) was added DMAP (183.32 mg, 1.50 mmol, 3.0 eq), EDCI (191.78 mg, 1.00 mmol, 2 eq) and DCM (3 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition H_2O 40 mL at 0 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 1:0 to 0:1) to afford methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (150 mg, 301.54 umol, 60.28% yield, 95% purity) as a yellow oil. MS (ESI) *m/z* 473.2 $[M+H]^+$

Step 6: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-4,4-dimethylpentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001515] A solution of methyl (2S)-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (130 mg, 275.09 umol, 1 eq) in NH_3/MeOH (7 M, 15 mL, 381.70 eq) was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, ethyl acetate:MeOH = 50:3) to afford product N-[(1S)-1-[[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-

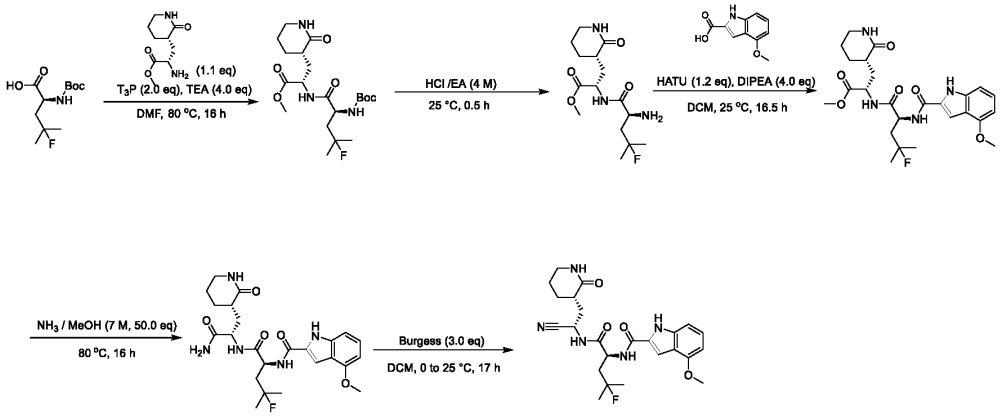
yl]methyl]ethyl]amino]methyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (60 mg, 131.13 umol, 47.67% yield) as a yellow solid. MS (ESI) *m/z* 458.3 $[M+H]^+$

Step 7: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)amino)-4,4-dimethylpentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001516] To a solution of N-[(1S)-1-[[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]methyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (50 mg, 109.27 umol, 1 eq) in EtOAc (2 mL) was added T_3P (2.14 g, 3.36 mmol, 2 mL, 50% purity, 30.77 eq) drop-wise, and then the resulting mixture was stirred at 65 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 um; mobile phase: [water (0.2% FA) - ACN]; B%: 15% - 45%, 8 min) and was separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 25% - 25%, 20 min) to afford N-[(1S)-1-[[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]methyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (4.4 mg, 9.92 umol, 29.07% yield, 99.1% purity) as a white solid. MS (ESI) *m/z* 440.2 $[M+H]^+$.

[0001517] ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.22 - 6.99 (m, 3 H) 6.52 (br d, *J*=7.72 Hz, 1 H) 4.74 - 4.65 (m, 1 H) 4.61 - 4.48 (m, 1 H) 4.03 - 3.91 (m, 4 H) 3.62 - 3.51 (m, 1 H) 3.47 - 3.36 (m, 1 H) 3.27 - 3.19 (m, 1 H) 2.50 - 2.41 (m, 1 H) 2.29 - 2.18 (m, 1 H) 1.81 (br s, 1 H) 1.74 - 1.64 (m, 2 H) 1.60 (br d, *J*=10.14 Hz, 1 H) 1.34 - 1.28 (m, 1 H) 0.98 (s, 9 H).

Example 190. Synthesis of viral protease inhibitor compound 667



Step 1: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4-fluoro-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001518] To a solution of compound (S)-2-((tert-butoxycarbonyl)amino)-4-fluoro-4-methylpentanoic acid (300.0 mg, 1.20 mmol, 1.0 *eq*) and compound methyl (S)-2-amino-3-((S)-2-oxopiperidin-3-yl)propanoate (313.3 mg, 1.32 mmol, 1.1 *eq*, HCl) in DMF (3 mL) was added T_3P (1.53 g, 2.41 mmol, 1.43 mL, 50% purity, 2.0 *eq*) and TEA (487.1 mg, 4.81 mmol, 0.67 mL, 4.0 *eq*). The mixture was stirred at 80 °C for 16 h. TLC (petroleum ether/ethyl acetate = 0/1, PMA). The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~1% MeOH/DCM @ 25 mL/min) to give methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-4-fluoro-4-methylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (620 mg, 1.15 mmol, 95.5% yield, 80% purity) as a yellow solid.

[0001519] LCMS: Rt = 0.773 min; for $C_{20}H_{34}FN_3O_6$ MS Calcd.: 431.24; MS Found: 432.2 $[M+H^+]$.

Step 2: Methyl (2S)-2-[[(2S)-2-amino-4-fluoro-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001520] A mixture of compound methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-4-fluoro-4-methylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (520 mg, 1.21 mmol, 1 *eq*) in HCl/EtOAc (4 mL) was stirred at 25 °C for 0.5 h. The mixture was concentrated under reduced pressure to give compound methyl (S)-2-((S)-2-amino-4-

fluoro-4-methylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (550 mg, crude, HCl, yellow oil) was used into the next step.

Step 3: Methyl (2S)-2-[[(2S)-4-fluoro-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4-methyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001521] To a solution of compound 4-methoxy-1H-indole-2-carboxylic acid (200 mg, 1.05 mmol, 1 *eq*) in DCM (5 mL) were added HATU (477.3 mg, 1.26 mmol, 1.2 *eq*) and DIEA (540.8 mg, 4.18 mmol, 0.73 mL, 4 *eq*). The mixture was stirred at 25 °C for 0.5 h. Compound methyl (S)-2-((S)-2-amino-4-fluoro-4-methylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (461.8 mg, 1.26 mmol, 1.2 *eq*, HCl) was added into the mixture. The mixture was stirred at 25 °C for 16 h. TLC (DCM/MeOH = 10/1, UV). The reaction mixture was diluted with H_2O (15 mL) and extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give methyl (S)-2-((S)-4-fluoro-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (480 mg, 83.9% yield) as a yellow solid.

[0001522] LCMS: Rt = 0.794 min; for $C_{25}H_{33}FN_4O_6$ MS Calcd.: 504.24; MS Found: 505.2 [$M+H^+$].

[0001523] ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 - 9.81 (m, 1H), 8.24 (br s, 1H), 7.23 - 7.06 (m, 3H), 7.01 (d, *J*= 8.28 Hz, 1H), 6.49 (d, *J* = 7.78 Hz, 1H), 6.17 (br s, 1H), 4.95 - 4.82 (m, 1H), 4.60 - 4.51 (m, 1H), 3.94 (s, 3H), 3.80 - 3.60 (m, 5H), 3.16 (br d, *J*=7.28 Hz, 2H), 3.00 - 2.77 (m, 1H), 1.98 (br d, *J*=6.02 Hz, 2H), 1.92 - 1.83 (m, 2H), 1.77 (br s, 2H), 1.51 - 1.44 (m, 6H).

Step 4: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3-fluoro-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[0001524] A solution of compound methyl (S)-2-((S)-4-fluoro-2-(4-methoxy-1H-indole-2-carboxamido)-4-methylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1 g, 1.98

mmol, 1 *eq*) in NH_3 (7 M in MeOH, 14.16 mL, 50 *eq*) was stirred at 80 °C for 16 h in a 30 mL of sealed tube. TLC (DCM/MeOH = 10/1, UV). The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~15% MeOH/Ethyl acetate @ 30 mL/min) to give compound N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-fluoro-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (370 mg, 0.74 mmol, 37.2% yield, 97.6% purity) as a yellow solid.

[0001525] LCMS: Rt = 0.743 min; for $C_{24}H_{32}FN_5O_5$ MS Calcd.: 489.24; MS Found: 490.2 $[M+H^+]$.

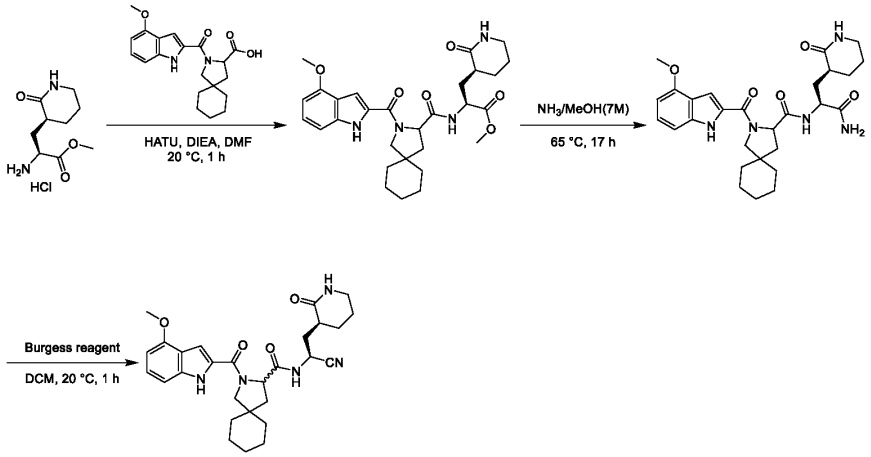
Step 5: N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3-fluoro-3-methyl-butyl]-4-methoxy-1H-indole-2-carboxamide

[0001526] To a solution of compound N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4-fluoro-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (350 mg, 0.71 mmol, 1 *eq*) in DCM (6 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (170.4 mg, 0.71 mmol, 1 *eq*) at 0 °C. The mixture was stirred at 25 °C for 0.5 h. Methoxycarbonyl-(triethylammonio)sulfonyl-azanide (170.4 mg, 0.71 mmol, 1 *eq*) was added into the mixture at 0 °C. The mixture was stirred at 25 °C for 0.5 h. methoxycarbonyl-(triethylammonio)sulfonyl-azanide (170.4 mg, 0.71 mmol, 1 *eq*) was added into the mixture at 0 °C. The mixture was stirred at 25 °C for 16 h. The mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (40 mL * 3). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was checked by LCMS. The residue was purified by *prep*-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water (0.05% NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 28%-58%, 7.8 min) to give N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-4-fluoro-4-methyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide (95 mg, 28.1% yield) as a white solid.

[0001527] LCMS: Rt = 0.780 min; for $C_{24}H_{30}FN_5O_4$ MS Calcd.: 471.23; MS Found: 472.2 $[M+H^+]$.

[0001528] ^1H NMR (400 MHz, CD_3OD) δ 7.24 - 7.20 (m, 1H), 7.18 - 7.11 (m, 1H), 7.07 - 7.01 (m, 1H), 6.51 (d, *J* = 7.78 Hz, 1H), 5.13 - 5.01 (m, 1H), 4.81 - 4.71 (m, 1H), 3.93 (s, 3H), 3.18 (dd, *J* = 7.40, 5.14 Hz, 2H), 2.49 - 2.34 (m, 2H), 2.32 - 2.11 (m, 2H), 2.00 - 1.87 (m, 2H), 1.83 - 1.73 (m, 1H), 1.72 - 1.60 (m, 1H), 1.54 - 1.37 (m, 7H).

Example 191. Synthesis of viral protease inhibitor compound 681



Step 1: (2S)-methyl 2-(2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001529] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 2.11 mmol, 1.1 *eq*, HCl) 2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (684.45 mg, 1.92 mmol, 1 *eq*) in DMF (15 mL) was added DIPEA (744.57 mg, 5.76 mmol, 1.00 mL, 3 *eq*) and HATU (730.19 mg, 1.92 mmol, 1 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the two batch reaction mixture was quenched by addition H_2O (80 mL), and extracted with ethyl acetate (40 mL * 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to get the product methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.35 g, crude) was obtained as white solid. MS (ESI) *m/z* 539.3 $[M+H]^+$.

Step 2: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001530] A solution of methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (650 mg, 1.21 mmol, 1 *eq*) in NH_3/MeOH (7 M, 3.45 mL, 20 *eq*) was stirred at 65 °C for 17 h. Upon completion, the two batch reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.22 g, crude) as a colorless oil. MS (ESI) *m/z* 524.3 $[M+H]^+$.

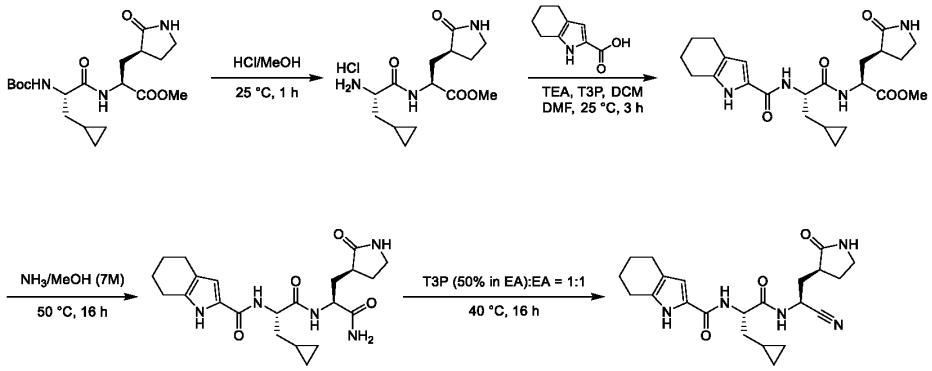
Step 3: N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001531] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.22 g, 2.33 mmol, 1 *eq*) in DCM (20 mL) was added Burgess reagent (1.39 g, 5.82 mmol, 2.5 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (3 mL) and then concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Agela DuraShell C18 250*70 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 43%-63%,20 min) to give desired compound (490 mg) as a white solid, which was further separated by SFC (column: DAICEL CHIRALPAK AD(250 mm*30 mm, 10 um);mobile phase: [0.1% NH_3H_2O IPA];B%: 58%-58%,10 min) to afford N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (201.77 mg, 394.36 umol, 16.93% yield, 98.820% purity) as a white solid. MS (ESI) *m/z* 506.3$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.26 (br s, 1 H) 8.50 - 8.85 (m, 1 H) 7.23 (br s, 1 H) 7.00 - 7.16 (m, 2 H) 6.89 (br s, 1 H) 6.52 (br d, J = 7.46 Hz, 1 H) 4.86 - 5.06 (m, 1 H) 4.48 - 4.79 (m, 1 H) 3.80 - 3.98 (m, 4 H) 3.59 (br d, J = 4.65 Hz, 1 H) 3.09 (br s, 2 H) 2.15 - 2.31 (m, 3 H) 1.73 - 2.01 (m, 2 H) 1.67 (br dd, J = 12.17, 8.62 Hz, 2 H) 1.33 - 1.61 (m, 12 H).

[0001532] N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 2 (200.95 mg, 394.35 umol,

16.93% yield, 99.222% purity) was obtained as a white solid. MS (ESI) *m/z* 506.3[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.27 (br s, 1 H) 8.61 (br d, *J* = 1.22 Hz, 1 H) 7.02 - 7.26 (m, 3 H) 6.91 (br s, 1 H) 6.53 (d, *J* =7.46 Hz, 1 H) 4.91 - 5.06 (m, 1 H) 4.62 (br s, 1 H) 3.82 - 3.98 (m, 4 H) 3.52 - 3.75 (m, 1 H) 3.09 (br s, 2 H) 2.09 - 2.28 (m, 3 H) 1.63 - 1.92 (m, 4 H) 1.33 - 1.62 (m, 12 H).

Example 192. Synthesis of viral protease inhibitor compound 711



Step 1: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001533] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (900 mg, 1.81 mmol, 80% purity, 1 *eq*) in HCl/MeOH (4 M, 12.00 mL, 26.50 *eq*) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to get product methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (600 mg, crude, HCl) as a white oil. MS (ESI) *m/z* 298.1 [M+H]$^+$.

Step 2: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-(4,5,6,7-tetrahydro-1H-indole-2-carbonylamino)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001534] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (600 mg, 1.80 mmol, 1 eq, HCl) in DCM (7 mL) and DMF (0.5 mL) was added 4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (415.68 mg, 2.52 mmol, 1.4 eq), TEA (1.09 g, 10.78 mmol, 1.50 mL, 6 eq) and T3P (1.72 g, 2.70 mmol, 1.60 mL, 50% purity, 1.5 eq). The mixture was stirred at 25 °C for 3 h. Upon

completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO2, DCM:MeOH = 10:1) and TLC (SiO2, DCM:MeOH = 10:1) to afford methyl (2S)-2-[[(2S)-3-cyclopropyl-2-(4,5,6,7-tetrahydro-1H-indole-2-carbonylamino)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (350 mg, 787.36 umol, 43.80% yield) as a yellow oil. MS (ESI) *m/z* 445.3 $[M+H]^+$.

Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide

[0001535] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-(4,5,6,7-tetrahydro-1H-indole-2-carbonylamino)propanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (350 mg, 787.36 umol, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 88.90 *eq*) was stirred at 50 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to afford N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide (300 mg, crude) as a yellow solid. MS (ESI) *m/z* 430.2 $[M+H]^+$.

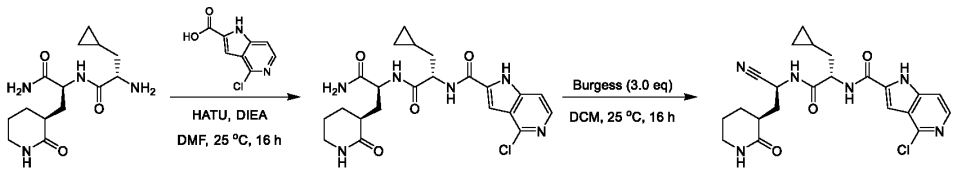
Step 4: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide

[0001536] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide (290 mg, 675.19 umol, 1 *eq*) in T3P (3 mL, 50% purity) and ethyl acetate (3 mL) was stirred at 40 °C for 16 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge BEH C18 100 * 25 mm * 5 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 25% - 55%, 10 min) to afford N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5,6,7-tetrahydro-1H-indole-2-carboxamide (61.92 mg, 150.48 umol, 22.29% yield, 100% purity) as a white solid. MS (ESI) *m/z* 412.3 $[M+H]^+$.

[0001537] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.96 (br s, 1H), 9.00 - 8.77 (m, 1H), 7.89 - 7.66 (m, 2H), 6.60 (br s, 1H), 5.04 - 4.81 (m, 1H), 4.48 - 4.28 (m, 1H), 3.24 - 3.04 (m, 2H), 2.47 - 1.96 (m, 7H), 1.81 - 1.61 (m, 7H), 1.40 (br dd, *J*=6.6, 13.1 Hz, 1H), 0.74 (br s, 1H), 0.38 (br s, 2H), 0.22 - -0.03 (m, 2H).

[0001538] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.67 (br s, 1H), 8.74 - 8.49 (m, 1H), 7.53 - 7.28 (m, 2H), 6.54 (d, *J*=2.2 Hz, 1H), 5.05 - 4.84 (m, 1H), 4.54 - 4.38 (m, 1H), 3.17 (br d, *J*=7.2 Hz, 2H), 2.54 (br t, *J*=6.1 Hz, 2H), 2.43 (br t, *J*=5.6 Hz, 3H), 2.28 - 2.08 (m, 2H), 1.90 - 1.79 (m, 1H), 1.77 - 1.65 (m, 6H), 1.56 (qd, *J*=6.7, 13.7 Hz, 1H), 0.83 - 0.70 (m, 1H), 0.42 (br d, *J*=7.8 Hz, 2H), 0.20 - 0.04 (m, 2H).

Example 193. Synthesis of viral protease inhibitor compound 715



Step 1: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[0001539] To a solution of 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid (110.5 mg, 0.56 mmol, 1 *eq*) in DMF (2 mL) was added HATU (256.6 mg, 0.67 mmol, 1.2 *eq*), DIEA (218.0 mg, 1.69 mmol, 0.29 mL, 3 *eq*) and (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (200 mg, 0.67 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 16 hr. LC-MS showed the desired compound was detected. TLC (DCM/MeOH = 10:1). The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic phase was washed with brine (10 mL * 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% DCM/MeOH ethergradient @ 20 mL/min) to afford *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxamide (214 mg, 76.2% yield) as a yellow solid.

Step 2: 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

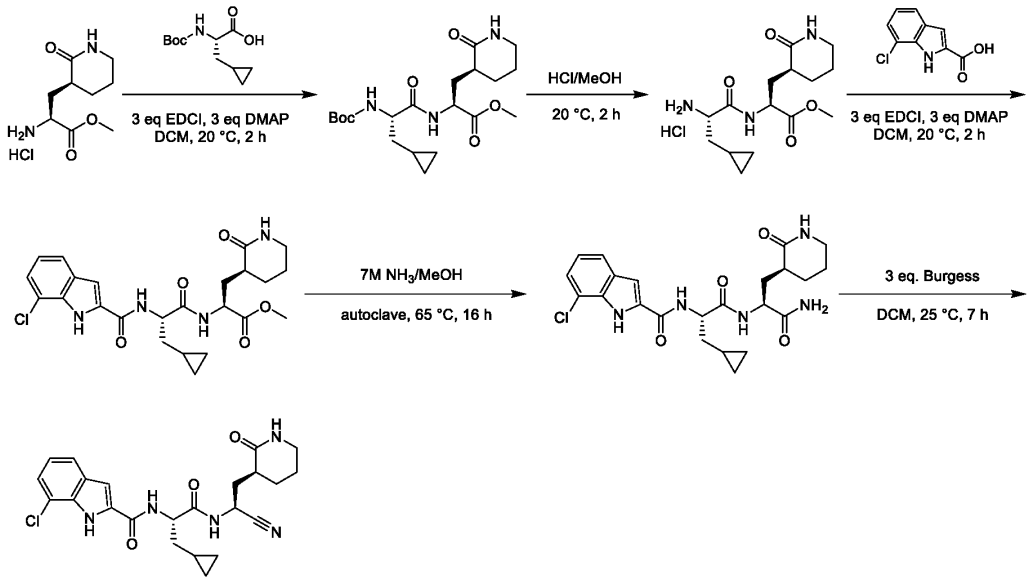
[0001540] To a solution of N-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxamide (214 mg, 0.45 mmol, 1 *eq*) in DCM (3 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (322.1 mg, 1.35 mmol, 3 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. TLC (DCM: MeOH = 10:1). The reaction mixture was filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% petroleum ether/ethyl acetate ethergradient @ 25 mL/min) to give 4-chloro-*N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxamide (80 mg, 36.5% yield) as a white solid.

[0001541] LCMS: Rt = 1.356 min; for $C_{22}H_{25}ClN_6O_3$ MS Calcd.: 456.17; MS Found: 457.1 [$M+H^+$].

[0001542] ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 - 8.65 (m, 1H), 7.53 - 7.43 (m, 1H), 7.41 - 7.31 (m, 1H), 5.14 (br d, *J* = 9.5 Hz, 1H), 4.54 (br t, *J* = 7.2 Hz, 1H), 3.24 (br s, 2H), 2.56 - 2.41 (m, 2H), 2.02 - 1.87 (m, 2H), 1.86 - 1.61 (m, 4H), 1.59 - 1.45 (m, 1H), 0.85 (br s, 1H), 0.54 (br d, *J* = 8.0 Hz, 2H), 0.23 - 0.15 (m, 2H).

Example 194. Synthesis of viral protease inhibitor compound 639

7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-indole-2-carboxamide



Step 1:

(S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001543] To a solution of (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (1.45 g, 6.34 mmol, 1.5 *eq*), methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 4.22 mmol, 1 eq, HCl), DMAP (1.55 g, 12.67 mmol, 3 eq) in DCM (10 mL) was added EDCI (2.43 g, 12.67 mmol, 3 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O 50 mL at 20 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL *2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 80/1 to 1/2) to give methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.5 g, 3.10 mmol, 73.34% yield, 85% purity) as a yellow oil. MS (ESI) *m/z* 412.2 $[M+H]^+$.

[0001544] To a solution of (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (29.06 g, 126.75 mmol, 1.5 *eq*), methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (20 g, 84.50 mmol, 1 ***eq***, HCl) and DMAP (25.81 g, 211.24 mmol, 2.5 eq) in DCM (200 mL), then EDCI (32.40 g, 168.99 mmol, 2.0 eq) was added. The

mixture was stirred at 20 °C for 2 hrs. The reaction mixture was quenched by addition H20 300 mL at 0 °C, and extracted with DCM 300 mL (100 mL * 3). The combined organic layers were washed with 0.5N HCl 100 mL and brine (100 mL * 2), dried over Na2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate = 10/1 to 1/2). To give methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (23 g, 54.83 mmol, 64.89% yield, 98.1% purity) was obtained as a white solid.

Step 2:

(S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001545] To a solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.5 g, 3.65 mmol, 1 eq) in HCl/MeOH (4 M, 15.00 mL, 16.46 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.27 g, crude, HCl) as a yellow oil. MS (ESI) *m/z* 312.2 $[M+H]^+$.

Step 3:

(S)-methyl 2-((S)-2-(7-chloro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001546] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.27 g, 3.65 mmol, 1 *eq*, HCl), 7-chloro-1H-indole-2-carboxylic acid (714.17 mg, 3.65 mmol, 1 *eq*), DMAP (1.34 g, 10.95 mmol, 3 *eq*) in DCM (13 mL) was added EDCI (1.75 g, 9.13 mmol, 2.5 *eq*) at 0 °C, the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O (20 mL) at 20 °C, and then extracted with DCM (25 mL * 3). The combined organic layers were washed with brine (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 80/1 to 1/0) to give methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-

propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.3 g, 2.53 mmol, 69.18% yield, 95% purity) as a yellow solid. MS (ESI) *m/z* 489.2 $[M+H]^+$.

Step 4:

N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-1H-indole-2-carboxamide

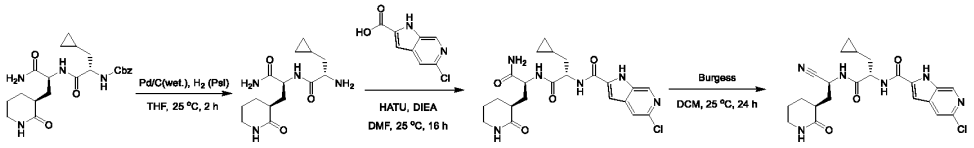
[0001547] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.3 g, 2.66 mmol, 1 *eq*) in NH_3/MeOH (7 M, 26 mL, 68.45 *eq*) was stirred at 65 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove solvent to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (1.26 g, crude) as a yellow solid. MS (ESI) *m/z* 474.2 $[M+H]^+$.

Step 5:

7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-indole-2-carboxamide

[0001548] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (1.26 g, 2.66 mmol, 1 *eq*) in DCM (13 mL) was added Burgess reagent (1.58 g, 6.65 mmol, 2.5 eq). The mixture was stirred at 25 °C for 7 h. Upon completion, the reaction mixture was concentrated by N2 remove solvent. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 0/1) to give 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (950 mg, crude) as a white solid. MS (ESI) *m/z* 456.2 $[M+H]^+$.

Example 195. Synthesis of viral protease inhibitor compound 717



Step 1: (2S)-2-amino-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide

[0001549] To a solution of benzyl *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (600 mg, 1.39 mmol, 1 *eq*) in THF (1 mL) was added Pd/C under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi or atm.) at 25 °C for 2 h. Pd/C was filtered and the reaction was concentrated under reduced pressure to give a residue. Compound (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (400 mg, crude) was obtained as a colorless oil.

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

[0001550] A solution of (2*S*)-2-amino-*N*-[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]-3-cyclopropyl-propanamide (250 mg, 0.84 mmol, 1 eq) in DMF (1 mL) was added HATU (320.7 mg, 0.84 mmol, 1 eq), 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (182.4 mg, 0.92 mmol, 1.1 eq) and DIEA (218.0 mg, 1.69 mmol, 0.29 mL, 2 eq) was stirred at 25 °C for 16 hr. TLC (DCM/MeOH = 10:1, I_2). The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL *3). The combined organic layers were washed with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 7% DCM/MeOH @ 35 mL/min). *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (260 mg, 64.3% yield, 99.2% purity) was obtained as a white solid.

Step 3: 5-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

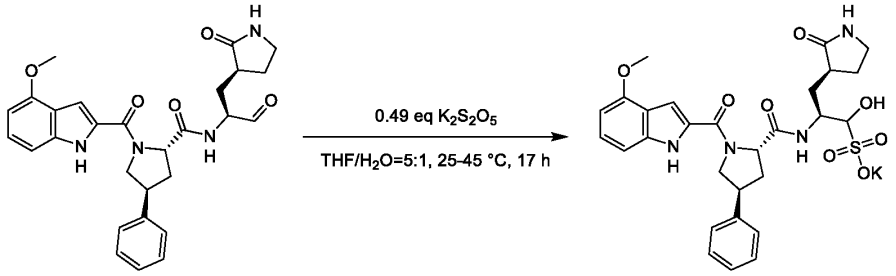
[0001551] To a solution of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (100 mg, 0.21 mmol, 1 eq) in DCM (1 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (150.5 mg, 0.63 mmol, 3 eq). The mixture was stirred at 25 °C for 24 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL *3). The combined organic layers were washed

with brine (30 mL *2), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80*40 mm*3 um; mobile phase: [water(0.05% NH_3H_2O + 10 mM NH_4HCO_3)-ACN];B%: 15%-45%, 9.5 min). 5-Chloro-*N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (94 mg, 96.7% yield, 99% purity) was obtained as a yellow solid.

[0001552] LCMS： Rt = 0.754 min; for $C_{22}H_{25}ClN_6O_3$ MS Calcd.: 456.93; MS Found: 457.1 [$M+H^+$].

[0001553] ^1H NMR (400MHz, CD_3OD) δ 8.58 (s, 1H), 7.72 - 7.65 (m, 1H), 7.20 (s, 1H), 5.13 (dd, *J* = 6.1, 10.2 Hz, 1H), 4.58 - 4.52 (m, 1H), 3.28 - 3.16 (m, 2H), 2.59 - 2.39 (m, 2H), 2.07 - 1.87 (m, 3H), 1.87 - 1.79 (m, 1H), 1.78 - 1.62 (m, 2H), 1.60 - 1.44 (m, 1H), 0.91 - 0.78 (m, 1H), 0.58 - 0.47 (m, 2H), 0.26 - 0.13 (m, 2H).

Example 196. Synthesis of viral protease inhibitor compound potassium (2S)-1-hydroxy-2-((2S,4S)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenylpyrrolidine-2-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate



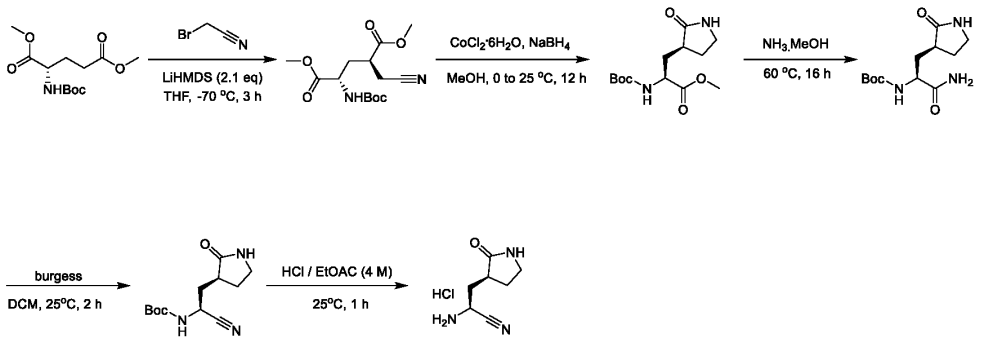
Step 1: [(2S)-1-hydroxy-2-[[(2S,4S)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propyl]sulfonyloxypotassium

[0001554] To a mixture of (2*S*,4*S*)-N-[(1*S*)-1-formyl-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carboxamide (40 mg, 79.59 umol, 1 *eq*) in THF (0.5 mL) was added $K_2S_2O_5$ (8.67 mg, 39.00 umol, 0.49 *eq*) in H_2O (0.1 mL) at 45 °C under N_2. The mixture was stirred at 45 °C for 3 h, and then stirred at 25 °C for 14 h under N_2. Upon completion, the reaction mixture was concentrated under reduced pressure, and then triturated with THF (1 mL) at 25 °C for 1 h to give [(2*S*)-1-

hydroxy-2-[[(2*S*,4*S*)-1-(4-methoxy-1H-indole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propyl]sulfonyloxypotassium (14.09 mg, 20.36 umol, 25.58% yield, 90% purity) as an off-white solid. MS (ESI) *m/z* 585.3 [M-36.8]$^{+}$.

[0001555] ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 11.68 - 11.40 (m, 1H), 8.08 - 7.64 (m, 0.5H), 7.52 - 7.43 (m, 0.5H), 7.41 - 7.29 (m, 4H), 7.28 - 7.19 (m, 1H), 7.15 - 6.97 (m, 2H), 6.96 - 6.76 (m, 1H), 6.55 - 6.37 (m, 1H), 5.48 - 5.27 (m, 1H), 5.25 - 4.92 (m, 0.5H), 4.80 - 4.60 (m, 0.5H), 4.46 - 4.07 (m, 2H), 4.02 - 3.93 (m, 0.5H), 3.93 - 3.63 (m, 5H), 3.62 - 3.36 (m, 1H), 3.18 - 3.02 (m, 1H), 2.94 - 2.69 (m, 0.5H), 2.35 - 2.17 (m, 3H), 2.10 - 1.87 (m, 1H), 1.82 - 1.27 (m, 3H).

Example 197. Synthesis of (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanenitrile hydrochloride



Step 1: (2S,4R)-dimethyl 2-((tert-butoxycarbonyl)amino)-4-(cyanomethyl)pentanedioate

[0001556] To a solution of dimethyl 2-(tert-butoxycarbonylamino)pentanedioate (10 g, 36.32 mmol, 1 eq) in THF (150 mL) was added LiHMDS (1 M, 83.55 mL, 2.3 eq) at -78 °C under N_2. The mixture was stirred at -78 °C for 1.5 h. Then, 2-bromoacetonitrile (6.54 g, 54.49 mmol, 3.63 mL, 1.5 eq) was added dropwise to the reaction at -78 °C. The mixture was stirred at -78 °C for 2.5 h. TLC (PE: EA=3:1, I_2). The reaction was completed, pre-cooled methanol (15 mL) and glacial acetic acid (12 mL) were sequentially added to quench the reaction. The reaction was warmed to 25 °C, and the solvent was distilled off under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~20% ethyl acetate/petroleum ether gradient @ 80 mL/min). Dimethyl (4R)-2-(tert-

butoxycarbonylamino)-4-(cyanomethyl)pentanedioate (15 g, 47.72 mmol, 43.79% yield) was obtained as a yellow oil.

Step 2: (S)-methyl2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001557] Dimethyl (4R)-2-(tert-butoxycarbonylamino)-4-(cyanomethyl)pentanedioate (15 g, 47.72 mmol, 1 eq) was dissolved in MeOH (250 mL), and $CoCl_2.6H_2O$ (6.81 g, 28.63 mmol, 0.6 eq) was added under 0 °C. After adding NaBH4 (10.83 g, 286.32 mmol, 6 eq) slowly in batches, the reaction was carried out at 25 °C for 12 h. TLC (petroleum ether/ethyl acetate = 1:2, I_2). After the reaction was completed, 100 mL of saturated ammonium chloride solution was added to quench the reaction. The organic phase was collected by filtration, the solvent was distilled off under reduced pressure, and extracted with EtOAc (150 mL * 3), and the organic phase was collected. The organic phase was washed with saturated brine (100 mL). The organic phase was dried over anhydrous Na_2SO_4, the filtrate was collected by filtration, and the solvent was evaporated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~80% ethyl acetate/petroleum ether gradient @ 40 mL/min). (S)-Methyl 2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (7 g, 24.45 mmol, 51.2% yield, 100% purity) was obtained as a white solid.

Step 3: tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate

[0001558] To a solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (2 g, 6.99 mmol, 1 eq) in MeOH (10 mL) was added a solution of NH_3 (7 M, 24.00 mL, 24.05 eq). The mixture was allowed to stir at 60 °C for 16 h in sealed tube. The reaction mixture was concentrated under reduced pressure to give a residue. Compound tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (1.8 g, 6.63 mmol, 94.9% yield) was obtained as a yellow solid.

Step 4: Tert-butyl ((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)carbamate

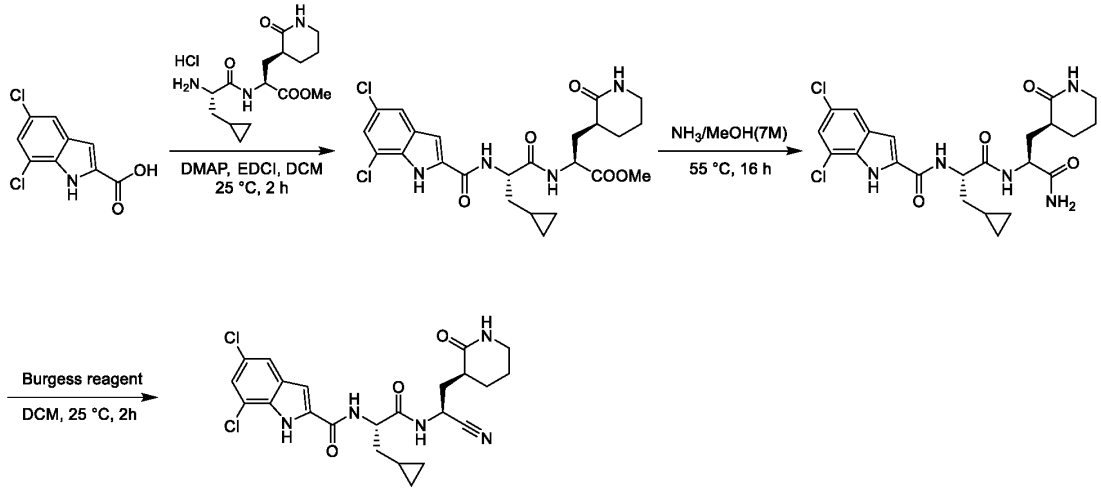
[0001559] To a solution of tert-butyl N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamate (1 g, 3.69 mmol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (3.51 g, 14.74 mmol, 4 *eq*). The mixture was stirred at 25 °C for 1 h under N_2. The reaction mixture was added H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4,

filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~70% ethyl acetate/petroleum ether gradient @ 30 mL/min). Compound tert-butyl N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamate (900 mg, 3.23 mmol, 87.7% yield, 91% purity) was obtained as a white solid.

Step 5: (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanenitrile hydrochloride

[0001560] To a solution of tert-butyl N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamate (600 mg, 2.37 mmol, 1 *eq*) in EtOAc (20 mL) was added HCl/EtOAc (4 M, 4.00 mL, 6.75 *eq*). The mixture was stirred at 25 °C for 2 h. LCMS showed starting material was consumed and detected desired compound. The reaction mixture was concentrated under reduced pressure to give a residue. Compound (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanenitrile (440 mg, 2.32 mmol, 97.9% yield, HCl) was obtained as a white solid.

Example 198. Synthesis of viral protease inhibitor compound 842



Step 1: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(5,7-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001561] To a mixture of 5,7-dichloro-1H-indole-2-carboxylic acid (1 g, 4.35 mmol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.35 g, 3.89 mmol, 8.95e-1 *eq*, HCl) in DCM (24 mL) was added DMAP (1.59 g, 13.04 mmol, 3 *eq*) and EDCI (1.67 g, 8.69 mmol, 2 *eq*) in one portion at

25 °C. The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL * 4). The combined organic layers were washed with brine (40 mL *1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3/1 to 0/1) to give methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(5,7-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.2 g, 2.29 mmol, 52.74% yield) as a white solid. MS (ESI) *m/z* 521.0 $[M-H]^+$

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5,7-dichloro-1H-indole-2-carboxamide

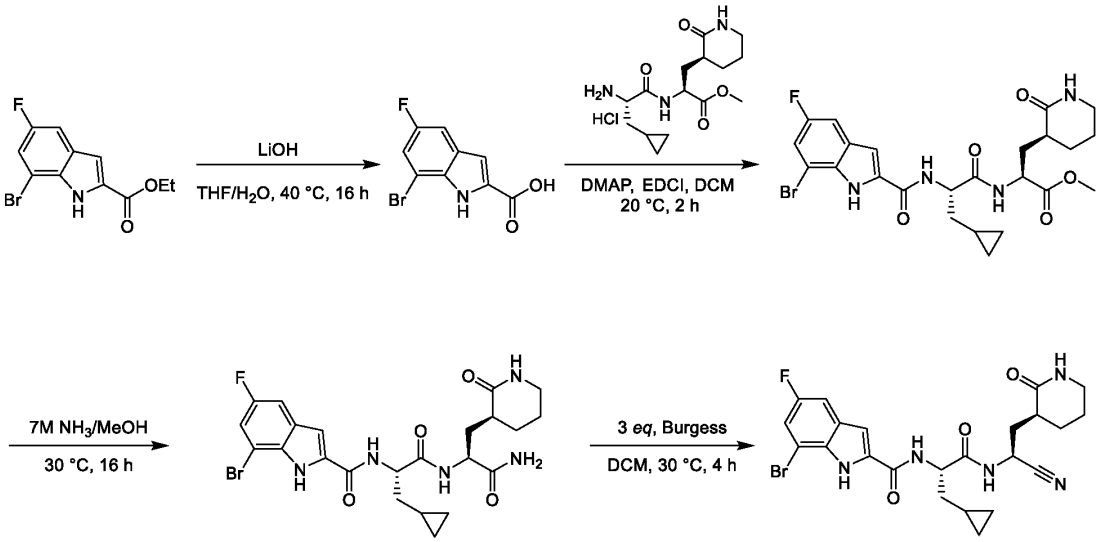
[0001562] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(5,7-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.2 g, 2.29 mmol, 1 *eq*) in NH_3/MeOH (7M, 30 mL) was stirred at 55 °C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5,7-dichloro-1H-indole-2-carboxamide (1 g, 1.97 mmol, 85.79% yield) as a white solid. MS (ESI) *m/z* 508.2 $[M+H]^+$

Step 3: 5,7-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001563] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5,7-dichloro-1H-indole-2-carboxamide (260 mg, 475.61 umol, 93% purity, 1 *eq*) in DCM (5 mL) was added Burgess reagent (226.68 mg, 951.23 umol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition; column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 40%-60%,8min) to give 5,7-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (100 mg, 203.92 umol, 42.88% yield) as a white solid. MS (ESI) *m/z* 490.1 $[M+H]^+$

[0001564] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.98 (br s, 1H), 9.00 (d, J=7.9 Hz, 1H), 8.77 (d, J=7.7 Hz, 1H), 7.75 (d, J=1.8 Hz, 1H), 7.54 (br s, 1H), 7.41 (d, J=1.8 Hz, 1H), 7.26 (s, 1H), 5.07 (q, J=8.0 Hz, 1H), 4.55 - 4.47 (m, 1H), 3.16 - 3.02 (m, 2H), 2.30 - 2.20 (m, 2H), 1.90 - 1.65 (m, 4H), 1.63 - 1.33 (m, 3H), 0.87 - 0.75 (m, 1H), 0.50 - 0.36 (m, 2H), 0.24 - 0.07 (m, 2H).

Example 199. Synthesis of viral protease inhibitor compound 852



Step 1: 7-bromo-5-fluoro-1H-indole-2-carboxylic acid

[0001565] To a solution of ethyl 7-bromo-5-fluoro-1*H*-indole-2-carboxylate (800 mg, 2.80 mmol, 1 *eq*) in THF (8 mL) and H_2O (4 mL) was added $LiOH{\cdot}H_2O$ (117.34 mg, 2.80 mmol, 1 *eq*) at 40 °C. The mixture was stirred at 40 °C for 16 h. Upon completion of reaction, the mixture was concentrated in vacuum and then the pH was adjusted to about 1 with 1 M HCl (10 mL), and was extracted with ethyl acetate (10 mL * 3) to obtain 7-bromo-5-fluoro-1*H*-indole-2-carboxylic acid (700 mg, crude) as a yellow solid. MS (ESI) *m/z* 256.0 $[M-H]^+$

Step 2: (S)-methyl2-((S)-2-(7-bromo-5-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001566] To a solution of methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxo-3- piperidyl] propanoate (800 mg, 2.30 mmol, 1 *eq*, HCl) and 7-bromo-5-

fluoro-1*H*-indole-2-carboxylic acid (700 mg, 2.76 mmol, 1.2 *eq*) in DCM (10 mL) was added DMAP (561.96 mg, 4.60 mmol, 2 *eq*), and then the mixture was added with EDCI (881.79 mg, 4.60 mmol, 2 *eq*). After stirring at 20 °C for 2 h, the mixture was poured into water (30 mL) and was extracted with DCM (10 mL * 3) and dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and was purified by column (SiO_2, PE/EA=1:0 to 0:1) to obtain (*S*)-methyl 2-((*S*)-2-(7-bromo -5-fluoro-1*H*-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1 g, 1.75 mmol, 76.09% yield, 96.5% purity) as a light yellow solid. MS (ESI) *m/z* 551.1 $[M+H]^+$

Step 3: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-bromo-5-fluoro-1H-indole-2-carboxamide

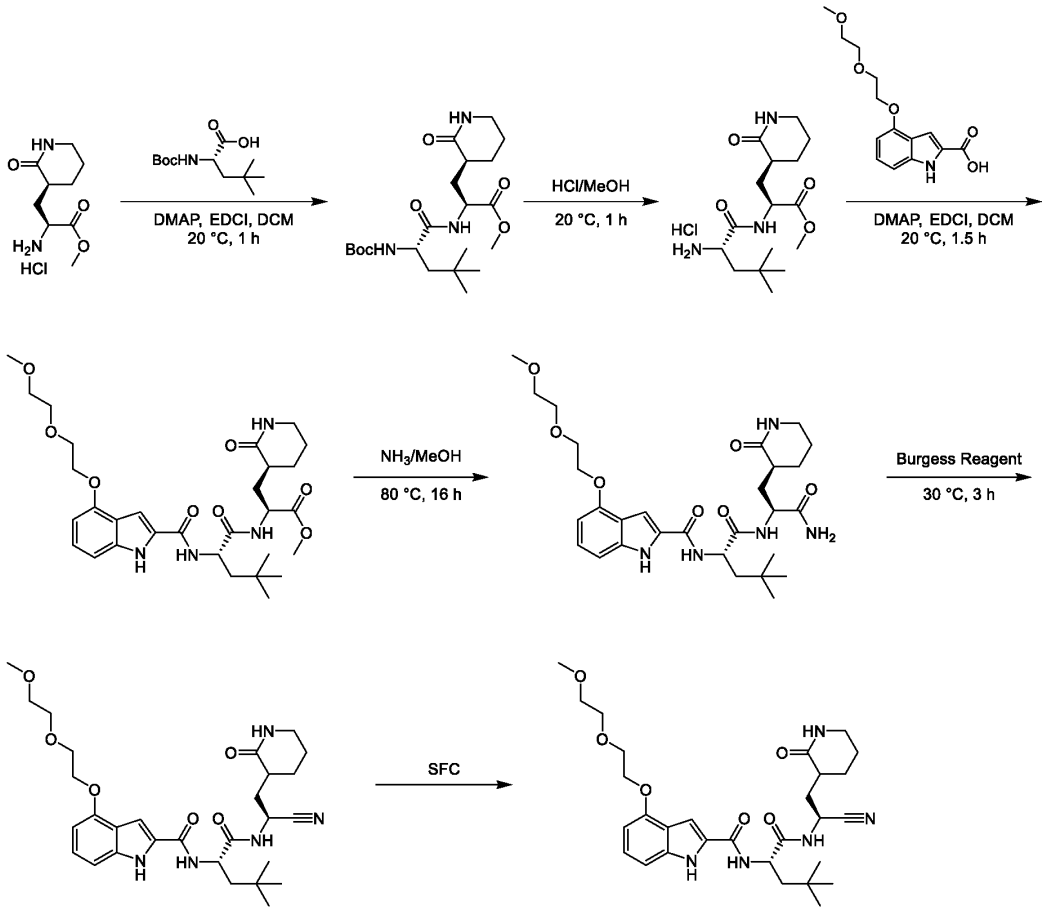
[0001567] A solution of (*S*)-methyl 2-((*S*)-2-(7-bromo-5-fluoro-1*H*-indole-2-carboxamido)-3- cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (1 g, 1.81 mmol, 1 *eq*) in NH_3/MeOH (30 mL, 7M) was stirred at 30 °C for 16 h. The mixture was concentrated in vacuum. Upon completion of reaction, the mixture was concentrtaed in vacuum to obtain *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-bromo-5-fluoro-1*H*-indole-2-carboxamide (800 mg, crude) as a light yellow solid. MS (ESI) *m/z* 536.2 $[M+H]^+$

Step 4: 7-bromo-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-fluoro-1H-indole-2-carboxamide

[0001568] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino) -3-cyclopropyl-1-oxopropan-2-yl)-7-bromo-5-fluoro-1*H*-indole-2-carboxamide (800 mg, 1.81 mmol, 1 *eq*) in DCM (10 mL) was added Burgess reagent (1.30 g, 5.44 mmol, 3 *eq*), and the mixture was stirred at 30 °C for 4 h. Upon completion of reaction, the reaction mixture was quenched by water (1 mL) and was dried with using N_2 and was purified by prep-HPLC (column: Welch Xtimate C18 250*70mm#10um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-60%, 20min) to obtain 7-bromo-*N*-((S)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-fluoro-1*H*-indole-2-carboxamide (740 mg, 1.33 mmol, 53.51% yield, 98% purity) as a white solid. MS (ESI) *m/z* 518.1 $[M+H]^+$

[0001569] ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 9.01 (d, J = 7.7 Hz, 1H), 8.81 (d, J = 7.5 Hz, 1H), 7.59 - 7.48 (m, 2H), 7.45 (dd, J = 2.4, 9.0 Hz, 1H), 7.26 (s, 1H), 5.07 (q, J = 7.8 Hz, 1H), 4.57 - 4.46 (m, 1H), 3.14 - 3.01 (m, 2H), 2.31 - 2.19 (m, 2H), 1.90 - 1.64 (m, 4H), 1.63 - 1.34 (m, 3H), 0.85 - 0.75 (m, 1H), 0.49 - 0.37 (m, 2H), 0.24 - 0.06 (m, 2H).

Example 200. Synthesis of viral protease inhibitor compound 876



Step 1: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001570] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.3 g, 5.49 mmol, 1 *eq*, HCl) in DCM (20 mL) was added (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (1.62 g, 6.59 mmol, 1.2 *eq*), DMAP (1.68 g, 13.73 mmol, 2.5 *eq*) and EDCI (2.11 g, 10.98 mmol, 2 *eq*). After stirring at 20 °C for 1 h, the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The

combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 6/1~4/1) to get product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.9 g, 4.00 mmol, 72.82% yield, 90% purity) as yellow oil. MS (ESI) *m/z* 428.3 $[M+H]^+$.

Step 2: methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001571] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.71 g, 5.69 mmol, 1 *eq*) in HCl/MeOH (4 M, 20.00 mL, 14.05 *eq*) was stirred at 20 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (30 mL * 3) and concentrated under reduced pressure to get the product methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.35 g, crude, HCl) as white oil. MS (ESI) *m/z* 328.3 $[M+H]^+$.

Step 3: methyl (2S)-2-[[(2S)-2-[[4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carbonyl]amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001572] A mixture of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.35 g, 3.71 mmol, 1 *eq*, HCl) in DCM (20 mL) then added 4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxylic acid (1.24 g, 4.45 mmol, 1.2 *eq*), DMAP (1.13 g, 9.28 mmol, 2.5 *eq*) and EDCI (1.42 g, 7.42 mmol, 2 *eq*) was stirred at 20 °C for 1.5 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 8/1~4/1) to get methyl (2S)-2-[[(2S)-2-[[4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carbonyl]amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (2.1 g, 2.85 mmol, 76.92% yield, 80% purity) as a yellow solid. MS (ESI) *m/z* 589.4 $[M+H]^+$.

Step 4: 2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[0001573] A mixture of methyl (2S)-2-[[(2S)-2-[[4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carbonyl]amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.52 g, 4 batches in parallel, 706.65 umol, 80% purity, 1 *eq*) in

NH_3/MeOH (7 M, 8 mL, 79.25 *eq*) was stirred at 80 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, and then was dissolved with DCM (30 mL * 3). The reaction was concentrated under reduced pressure to afford N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide (1.3 g, crude) as a white solid. MS (ESI) *m/z* 574.4 $[M+H]^+$.

Step 5: N-[1-[[1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide

[0001574] A mixture of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide (1.1 g, 1.92 mmol, 1 *eq*) in DCM (15 mL) was added with BURGESS REAGENT (1.37 g, 5.76 mmol, 3 *eq*). The resulting mixture was stirred at 30 °C for 3 h. Upon completion, the mixture were quenched with water (1 mL) and dried with using N_2. The residue was purified by prep-HPLC (column: Waters X bridge C18 150 * 50 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 10 min), which was further separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [Neu-ETOH]; B%: 53% - 53%, 10 min): to afford N-[1-[[1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide Isomer 1 (250.32 mg, 450.49 umol, 23.46% yield) as a white solid. MS (ESI) *m/z* 556.3 $[M+H]^+$.

[0001575] ^1H NMR (400 MHz, MeOD-d_4) δ = 7.29 (s, 1H), 7.17 - 7.10 (m, 1H), 7.07 - 7.01 (m, 1H), 6.52 (d, *J*=7.5 Hz, 1H), 5.08 (dd, *J*=6.2, 9.9 Hz, 1H), 4.64 (dd, *J*=4.2, 8.6 Hz, 1H), 4.29 - 4.23 (m, 2H), 3.93 (dd, *J*=4.0, 5.3 Hz, 2H), 3.79 - 3.74 (m, 2H), 3.62 - 3.54 (m, 2H), 3.37 (s, 3H), 3.23 - 3.14 (m, 2H), 2.49 - 2.37 (m, 2H), 2.00 - 1.41 (m, 7H), 1.03 (s, 9H).

[0001576] N-[1-[[1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide Isomer 2 (27.92 mg, 50.25 umol, 2.62% yield) was obtained as a white solid. MS (ESI) *m/z* 556.3 $[M+H]^+$.

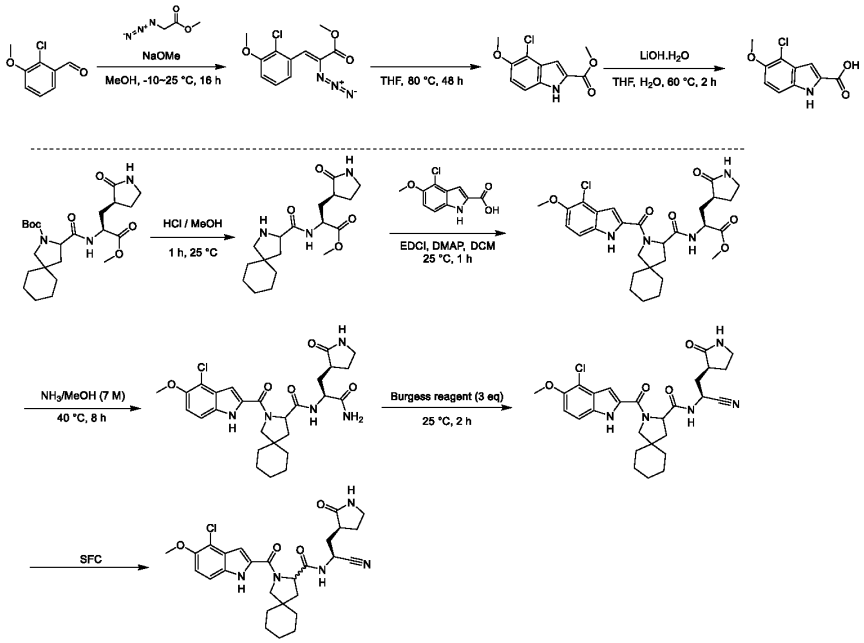
[0001577] ^1H NMR (400 MHz, MeOD-d_4) δ = 7.29 (d, *J*=0.9 Hz, 1H), 7.17 - 7.11 (m, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 6.52 (d, *J*=7.5 Hz, 1H), 5.08 (dd, *J*=5.8, 8.0 Hz, 1H), 4.68 (dd,

J=4.0, 8.8 Hz, 1H), 4.30 - 4.23 (m, 2H), 3.93 (dd, *J*=3.9, 5.2 Hz, 2H), 3.80 - 3.73 (m, 2H), 3.62 - 3.56 (m, 2H), 3.37 (s, 3H), 3.22 - 3.13 (m, 2H), 2.45 - 2.28 (m, 2H), 2.01 - 1.76 (m, 5H), 1.71 - 1.49 (m, 2H), 1.02 (s, 9H).

[0001578] N-[1-[[1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide Isomer 3 (31.42 mg, 56.54 umol, 2.95% yield) was obtained as a a white solid. MS (ESI) *m/z* 556.3 $[M+H]^+$.

[0001579] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.30 (d, *J*=0.9 Hz, 1H), 7.13 (d, *J*=7.7 Hz, 1H), 7.08 - 7.01 (m, 1H), 6.53 (d, *J*=7.3 Hz, 1H), 5.01 (s, 1H), 4.65 (s, 1H), 4.30 - 4.23 (m, 2H), 3.93 (dd, *J*=4.0, 5.3 Hz, 2H), 3.81 - 3.73 (m, 2H), 3.63 - 3.55 (m, 2H), 3.37 (s, 3H), 3.21 (br d, *J*=4.6 Hz, 2H), 2.49 - 2.37 (m, 1H), 2.34 - 2.23 (m, 1H), 1.97 - 1.88 (m, 2H), 1.87 - 1.63 (m, 4H), 1.58 - 1.45 (m, 1H), 1.02 (s, 9H).

Example 201. Synthesis of viral protease inhibitor compound 880



Step 1: methyl (Z)-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate

[0001580] A mixture 2-chloro-3-methoxy-benzaldehyde (4 g, 23.45 mmol, 1 *eq*) and NaOMe (2.53 g, 46.90 mmol, 2 *eq*) with MeOH (20 mL) was cooled to -10 °C, and then a mixture of methyl azide acetate (5.49 g, 46.90 mmol, 2 *eq*) in MeOH (50 mL) was added

dropwise. The mixture was stirred at 25 °C for 16 h and white solid was observed. Upon completion, the reaction mixture was filtered to give the compound methyl (Z)-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate (3 g, 10.09 mmol, 43.02% yield, 90% purity) as a white solid. MS (ESI) *m/z* 267.0 $[M+H]^+$

Step 2: methyl 4-chloro-5-methoxy-1H-indole-2-carboxylate

[0001581] To a solution of methyl (*Z*)-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate (1 g, 3.74 mmol, 1 *eq*) in THF (30 mL) was added bis(trifluoromethylsulfonyloxy)iron (2.64 g, 7.47 mmol, 2 *eq*) and the mixture was stirred at 80 °C for 48 h. Upon completion, the reaction was concentrated in the vacuum and quenched by addition H_2O (100 mL) and then extracted with DCM (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 5/1) to afford methyl 4-chloro-5-methoxy-1H-indole-2-carboxylate (140 mg, 584.17 umol, 15.64% yield) was a brown solid. MS (ESI) *m/z* 240.0 $[M+H]^+$

Step 3: 4-chloro-5-methoxy-1H-indole-2-carboxylic acid

[0001582] To a solution of methyl 4-chloro-5-methoxy-1H-indole-2-carboxylate (0.55 g, 2.29 mmol, 1 *eq*) in THF (5 mL), H_2O (2.5 mL) was added $LiOH \cdot H_2O$ (96.31 mg, 2.29 mmol, 1 *eq*), and the mixture was stirred at 60 °C for 2 h. Upon completion, the pH of the reaction mixture was adjusted to ~3 with HCl. The mixture was extracted with ethyl acetate (100 mL * 3). The combined organic layer was dried over Na_2SO_4, filtered, concentrated to give 4-chloro-5-methoxy-1H-indole-2-carboxylic acid (340 mg, crude) as a brown solid. MS (ESI) *m/z* 226.0 $[M+H]^+$

Step 4: (2S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate

[0001583] A solution of *tert*-butyl 3-(((*S*)-1-methoxy-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate (1.3 g, 2.88 mmol, 1 *eq*) in HCl/MeOH (15 mL) was stirred for 1 h at 25 °C. Upon completion, the mixture was quenched by the addition $NaHCO_3$ (200 mL) and then extracted with DCM (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude product (2*S*)-methyl 3-

((*S*)-2-oxopyrrolidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate (1.1 g, crude) was yellow solid. MS (ESI) *m/z* 352.2 $[M+H]^+$

Step 5: (2S)-methyl 2-(2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001584] To a solution of (2*S*)-methyl 3-((*S*)-2-oxopyrrolidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate (934.56 mg, 2.66 mmol, 1 *eq*) in DCM (20 mL) was added 4-chloro-5-methoxy-1H-indole-2-carboxylic acid (600 mg, 2.66 mmol, 1 *eq*), EDCI (1.02 g, 5.32 mmol, 2 *eq*), and DMAP (974.62 mg, 7.98 mmol, 3 *eq*). After stirring the mixture at 25 °C for 1 h, the reaction was quenched by addition H_2O (200 mL) and then extracted with ethyl acetate (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to afford (2*S*)-methyl 2-(2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (1.2 g, 1.93 mmol, 72.57% yield, 89.9% purity) as a yellow solid. MS (ESI) *m/z* 559.2 $[M+H]^+$

Step 6: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001585] A solution of (2*S*)-methyl 2-(2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (1.2 g, 2.15 mmol, 1 *eq*) in NH_3 (in MeOH, 7 M, 30 mL, 97.83 *eq*) was stirred at 40 °C for 8 h. Upon completion, the reaction was concentrated in the vacuum to give crude product N-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.15 g, crude) as a yellow solid. MS (ESI) *m/z* 544.2 $[M+H]^+$

Step 7: (2S)-methyl 2-(2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001586] To a solution of N-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.15 g, 2.11 mmol, 1 *eq*) in DCM (20 mL) was added BURGESS REAGENT (1.51 g, 6.34 mmol, 3 *eq*), and the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was purified by prep-HPLC (column: Waters Xbridge C18 150*50mm*

10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-65%,10min) to give 2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (400 mg, 760.42 umol, 35.97% yield) as a white solid. MS (ESI) *m/z* 526.2 $[M+H]^+$

Step 8: (2S)-methyl 2-(2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001587] 2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide was separated by SFC (column: DAICEL CHIRALPAK AS(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O MEOH];B%: 43%-43%,8min) to afford 2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (170 mg, 323.18 umol, 42.50% yield, 100% purity) as a white solid. MS (ESI) *m/z* 526.2 $[M+H]^+$

[0001588] ^1H NMR (400MHz, DMSO-d_6) δ = 11.80 - 11.70 (m, 1H), 9.07 - 8.78 (m, 1H), 7.72 - 7.50 (m, 1H), 7.41 - 7.33 (m, 1H), 7.21 - 7.12 (m, 1H), 6.92 - 6.57 (m, 1H), 5.00 - 4.89 (m, 1H), 4.82 - 4.46 (m, 1H), 3.88 - 3.81 (m, 4H), 3.73 - 3.38 (m, 1H), 3.17 - 2.90 (m, 2H), 2.40 - 2.20 (m, 2H) 2.17 - 2.05 (m, 2H), 1.82 - 1.64 (m, 2H), 1.61 - 1.51 (m, 2H), 1.49 - 1.27 (m, 9H)

[0001589] ^1H NMR (400MHz, DMSO-d_6) δ = 11.52 (br s, 1H), 8.65 (br s, 1H), 7.40 - 7.39 (m, 2H), 7.16 - 7.13(m, 1H), 6.86 (br s, 1H), 4.94 (br s, 1H), 4.59 (br s, 1H), 3.90 - 3.68 (m, 5H), 3.15 - 3.06(m, 2H), 2.26 - 2.05 (m, 4H), 1.80 (br s, 1H), 1.68 (br s, 1H), 1.56 - 1.52(m, 3H), 1.45 - 1.40(m, 8H)

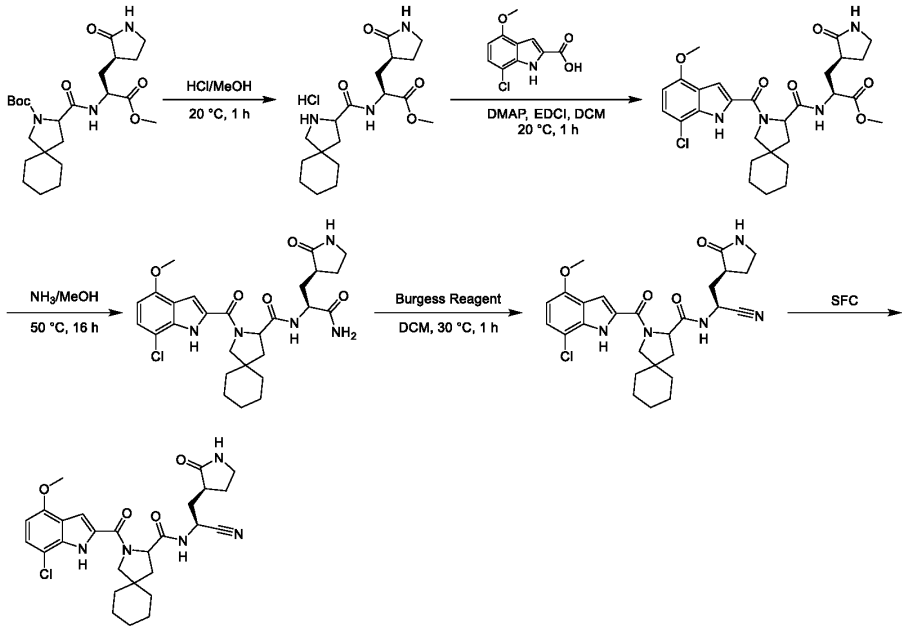
[0001590] 2-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (170 mg, 323.18 umol, 42.50% yield, 100% purity) was obtained as white solid. MS (ESI) *m/z* 526.2 $[M+H]^+$

[0001591] ^1H NMR (400MHz, DMSO-d_6) δ = 11.79 - 11.65 (m, 1H), 9.10 - 8.87 (m, 1H), 7.75 - 7.55 (m, 1H), 7.43 - 7.27 (m, 1H), 7.21 - 7.08 (m, 1H), 6.93 - 6.58 (m, 1H), 4.99 - 4.94(m, 1H), 4.69 - 4.44 (m, 1H), 3.92 - 3.79 (m, 4H), 3.77 - 3.67 (m, 1H), 3.31 - 3.06 (m,

2H), 2.48 - 2.34 (m, 1H), 2.46 - 2.34 (m, 1H), 2.20 - 2.05 (m, 2H), 1.97 - 1.64 (m, 2H), 1.63 - 1.52 (m, 2H), 1.50 - 1.29 (m, 9H)

[0001592] 1H NMR (400MHz, DMSO-d_6) δ = 11.52 (br s, 1H), 8.75 (br s, 1H), 7.57 - 7.34 (m, 2H), 7.15 - 7.13 (m, 1H), 6.84 (br s, 1H), 4.91 (br s, 1H), 4.61 (br s, 1H), 3.86 - 3.68 (m, 5H), 3.17 - 3.09 (m, 2H), 2.43 - 2.02 (m, 4H), 1.81 (br s, 1H), 1.67 (br s, 1H), 1.53 (br s, 3H), 1.45 - 1.41 (m, 8H)

Example 202. Synthesis of viral protease inhibitor compound 882



Step 1: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001593] A mixture of tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (1.5 g, 3.32 mmol, 1 *eq*) in HCl/MeOH (4 M, 20 mL, 24.08 *eq*) was stirred at 20 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (30 mL * 3) and concentrated under reduced pressure to get product methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.29 g, crude, HCl) as a white oil MS (ESI) *m/z* 352.2 $[M+H]^+$.

Step 2: methyl (2S)-2-[[2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001594] To a mixture of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.24 g, 3.20 mmol, 1 *eq*, HCl) in DCM (15 mL) was added 7-chloro-4-methoxy-1H-indole-2-carboxylic acid (865.52 mg, 3.84 mmol, 1.2 *eq*), DMAP (976.35 mg, 7.99 mmol, 2.5 *eq*) and EDCI (1.23 g, 6.39 mmol, 2 *eq*). The resulting mixture was stirred at 20 °C for 1 h, and then the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 8/1~5/1) to afford methyl (2S)-2-[[2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.6 g, 2.46 mmol, 77.00% yield, 86% purity) as a yellow oil. MS (ESI) *m/z* 559.3 $[M+H]^+$.

Step 3: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001595] A mixture of methyl (2S)-2-[[2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (400 mg, 4 batches in parallel, 615.33 umol, 86% purity, 1 *eq*) in NH_3/MeOH (7 M, 20 mL, 227.52 *eq*) was stirred at 50 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.3 g, crude) as yellow solid. MS (ESI) *m/z* 544.3 $[M+H]^+$.

Step 4: 2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[0001596] To a mixture of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.2 g, 2.21 mmol, 1 *eq*) in DCM (15 mL) was added BURGESS REAGENT (1.58 g, 6.62 mmol, 3 *eq*). After stirring at 30 °C for 1 h, the mixture was quenched with water (1 mL) and dried with using N_2. The residue was purified by prep-

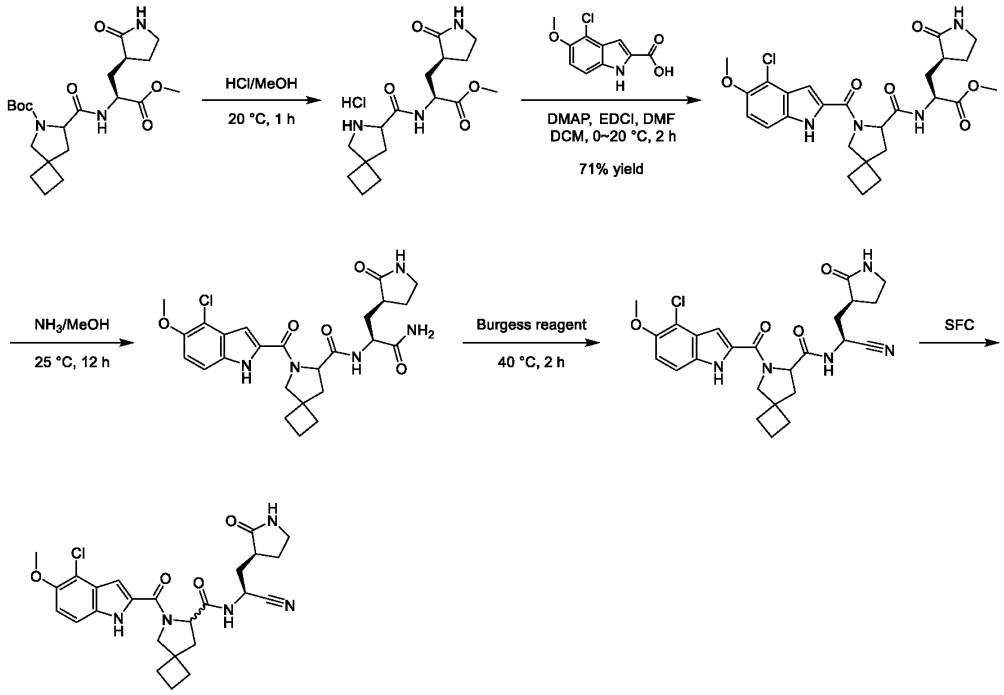
HPLC (column: Waters X bridge C18 150 * 50 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 35% - 65%, 10 min), which was further separated by SFC (column: DAICEL CHIRALPAK IC (250 mm * 30 mm, 10 um); mobile phase: [Neu - IPA]; B%: 60% - 60%, 9 min) to afford 2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (378.42 mg, 719.39 umol, 32.62% yield, 100% purity) as a white solid. MS (ESI) *m/z* 526.2 $[M+H]^+$.

[0001597] ^1H NMR (400 MHz, MeOD-d_4) δ = 7.20 - 7.13 (m, 1H), 7.11 (s, 1H), 6.59 - 6.42 (m, 1H), 5.11 - 5.02 (m, 1H), 4.80 - 4.58 (m, 1H), 3.99 - 3.89 (m, 3H), 3.89 - 3.82 (m, 1H), 3.77 - 3.38 (m, 1H), 3.28 (br s, 1H), 2.99 - 2.66 (m, 1H), 2.52 - 2.25 (m, 3H), 2.17 - 1.69 (m, 3H), 1.65 - 1.26 (m, 11H).

[0001598] 2-(7-Chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide Isomer 2 (367.22 mg, 698.10 umol, 31.65% yield, 100% purity) was obtained as a white solid. MS (ESI) *m/z* 526.2 $[M+H]^+$.

[0001599] ^1H NMR (400 MHz, MeOD-d_4) δ = 7.18 (d, *J*=8.2 Hz, 1H), 7.14 (s, 1H), 6.54 (d, *J*=8.3 Hz, 1H), 5.03 (dd, *J*=6.0, 10.1 Hz, 1H), 4.63 (dd, *J*=7.8, 9.7 Hz, 1H), 3.99 - 3.88 (m, 4H), 3.76 (d, *J*=10.3 Hz, 1H), 3.30 - 3.23 (m, 1H), 2.53 - 2.40 (m, 1H), 2.39 - 1.96 (m, 3H), 1.95 - 1.70 (m, 3H), 1.68 - 1.38 (m, 11H).

Example 203. Synthesis of viral protease inhibitor compound 886



Step 1: (2S)-methyl 3-((S)-2-oxopyrrolidin-3-yl)-2-(6-azaspiro[3.4]octane-7-carboxamido)propanoate hydrochloride

[0001600] A solution of tert-butyl 7-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (1.5 g, 3.54 mmol, 1 eq) in HCl/MeOH (4 M, 37.50 mL, 42.35 eq) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.2 g, crude, HCl) as a white solid.

Step 2: (2S)-methyl 2-(6-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[0001601] To a solution of methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.1 g, 3.06 mmol, 1 eq, HCl) and 4-chloro-5-methoxy-1H-indole-2-carboxylic acid (700 mg, 3.10 mmol, 1.01 eq) in DMF (7 mL) and DCM (30 mL) at 0 °C was added DMAP (1.12 g, 9.17 mmol, 3 eq) and EDCI (1.17 g, 6.11 mmol, 2 eq), and then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 100 mL at 0 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine 50 mL,

dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 5:1 to 0:1) to give methyl (2S)-2-[[6-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.2 g, 2.19 mmol, 71.71% yield, 97% purity) as a yellow solid. MS (ESI) *m/z* 531.2 $[M+H]^+$.

Step 3: N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-6-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[0001602] A solution of methyl (2S)-2-[[6-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.2 g, 2.26 mmol, 1 eq) in NH_3/MeOH (7 M, 50 mL, 154.87 eq) was stirred at 25 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-6-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (1.1 g, crude) as a yellow solid. MS (ESI) *m/z* 516.2 $[M+H]^+$.

Step 4: 6-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-6-azaspiro[3.4]octane-7-carboxamide

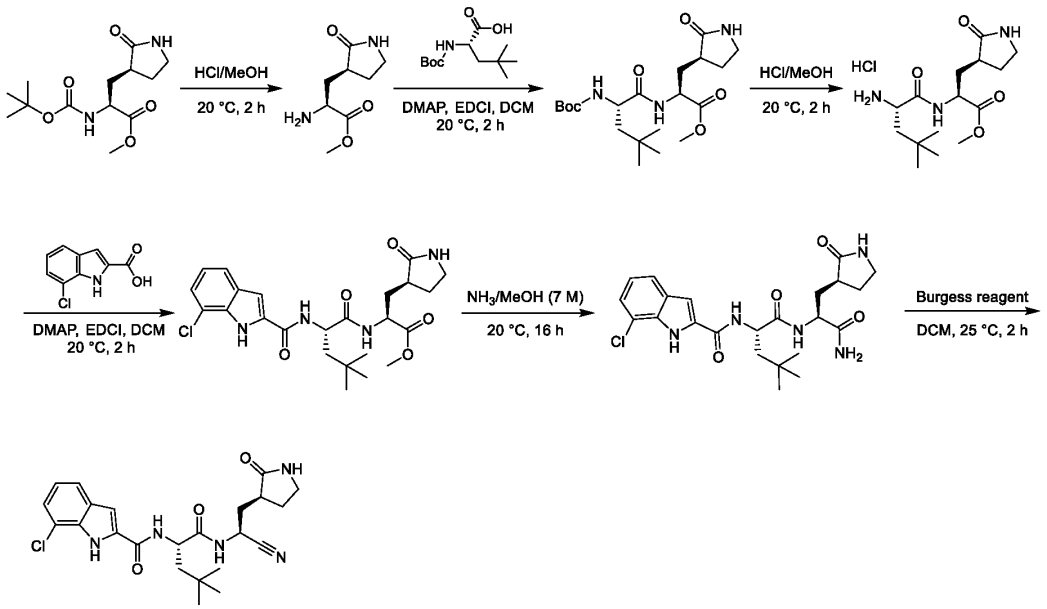
[0001603] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-6-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (1.1 g, 2.13 mmol, 1 eq) in DCM (40 mL) was added BURGESS REAGENT (1.27 g, 5.33 mmol, 2.5 eq), and then the mixture was stirred at 40 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Titank C18 Bulk 250 * 70 mm 10 u; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 6% - 36%, 20 min) to give desired compound (500 mg, 47% yield, 99% purity) as a white solid, which was further separated by SFC (column: DAICEL CHIRALPAK AS (250 mm * 30 mm, 10 um); mobile phase: [Neu-MeOH]; B%: 55% - 55%, 7 min) to afford 6-(4-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide Isomer 1 (232.45 mg, 466.79 umol, 21.90% yield, 100% purity) as a white solid. MS (ESI) *m/z* 498.2 $[M+H]^+$.

[0001604] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.85 - 11.68 (m, 1H), 9.09 - 8.67 (m, 1H), 7.74 - 7.42 (m, 1H), 7.42 - 7.32 (m, 1H), 7.21 - 7.10 (m, 1H), 7.01 - 6.46 (m, 1H), 5.02 - 4.40 (m, 2H), 4.11 - 3.65 (m, 5H), 3.20 - 2.90 (m, 2H), 2.36 - 1.63 (m, 13H)

[0001605] 6-(4-Chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide Isomer 2 (232.89 mg, 467.68 umol, 21.94% yield, 100% purity) was obtained as a white solid. MS (ESI) *m/z* 498.2 $[M+H]^+$.

[0001606] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.79 - 11.70 (m, 1H), 9.19 - 8.76 (m, 1H), 7.76 - 7.60 (m, 1H), 7.42 - 7.29 (m, 1H), 7.20 - 7.08 (m, 1H), 6.96 - 6.48 (m, 1H), 5.04 - 4.37 (m, 2H), 4.05 - 3.78 (m, 5H), 3.18 - 2.92 (m, 2H), 2.43 - 1.79 (m, 13H)

Example 204. Synthesis of viral protease inhibitor compound 888



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001607] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (20 g, 69.85 mmol, 1 eq) in HCl/MeOH (200 mL) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (13 g, crude, HCl) as a white solid. MS (ESI) *m/z* 187.1 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001608] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (13 g, 58.38 mmol, 1 eq, HCl) and (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (14.32 g, 58.38 mmol, 1 eq) in DCM (200 mL) was added DMAP (21.40 g, 175.15 mmol, 3 eq), and then EDCI (33.58 g, 175.15 mmol, 3 eq) was added. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 100 mL, and then extracted with DCM 100 mL (50 mL * 2). The combined organic layers were washed with HCl (1M) 100 mL (50 mL * 2), then were washed with brine 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1 to 0/1) to give methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (23 g, 50.62 mmol, 86.70% yield, 91% purity) as a white solid. MS (ESI) *m/z* 414.3 $[M+H]^+$

Step 3: methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001609] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (23 g, 55.62 mmol, 1 eq) in HCl/MeOH (200 mL) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (19 g, crude, HCl) as a yellow solid. MS (ESI) *m/z* 314.2 $[M+H]^+$

Step 4: methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001610] A solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1 g, 2.86 mmol, 1 eq, HCl) and 7-chloro-1H-indole-2-carboxylic acid (559.10 mg, 2.86 mmol, 1 eq) in DCM (40 mL) was added with DMAP (1.05 g, 8.58 mmol, 3 eq). After the addition of EDCI (1.64 g, 8.58 mmol, 3 eq), the resulting mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL), and then extracted with DCM 40 mL (20 mL *

2). The combined organic layers were washed with HCl (1M) 30 mL (15 mL * 2), the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1 to 0/1) to afford methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (930 mg, 1.84 mmol, 64.28% yield, 97% purity) as a white solid. MS (ESI) *m/z* 491.2 $[M+H]^+$.

Step 5: N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-chloro-1H-indole-2-carboxamide

[0001611] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (900 mg, 1.83 mmol, 1 eq) in NH_3/MeOH (7 M, 30 mL, 114.56 eq) was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-chloro-1H-indole-2-carboxamide (770 mg, crude) as a white solid. MS (ESI) *m/z* 476.2$[M+H]^+$.

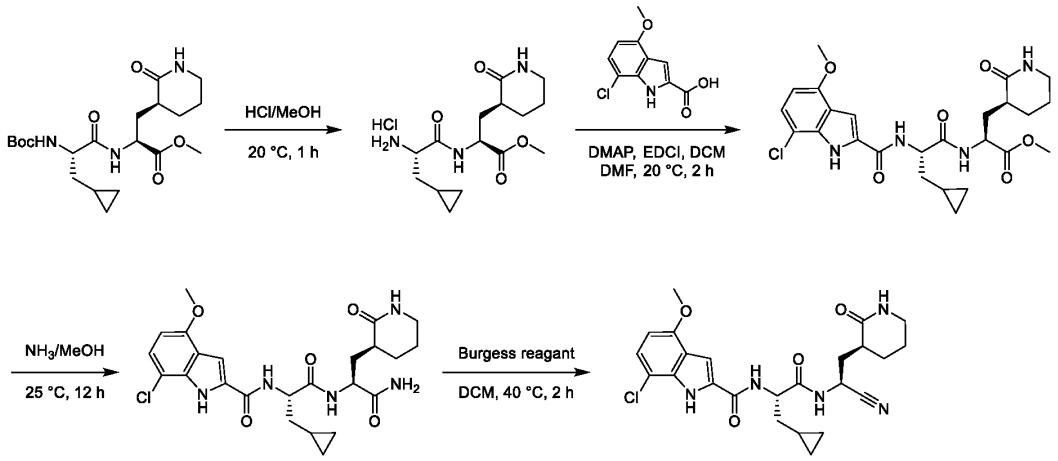
Step 6: 7-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1H-indole-2-carboxamide

[0001612] To a solution of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-chloro-1H-indole-2-carboxamide (760 mg, 1.60 mmol, 1 eq) in DCM (15 mL) was added Burgess reagent (761.03 mg, 3.19 mmol, 2 eq). The mixture was stirred at 25 °C for 2 h, and then the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150*50mm* 10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-55%,10min) to give 7-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-1H-indole-2-carboxamide (421 mg, 919.31 umol, 57.57% yield, 100% purity) as a white solid. MS (ESI) *m/z* 458.2$[M+H]^+$.

[0001613] 1H NMR (400MHz, DMSO-d_6) δ = 11.70 (s, 1H), 9.01 (d, *J* = 7.8Hz, 1H), 8.72 (d, *J* = 8.1Hz, 1H), 7.74 - 7.58 (m, 2H), 7.37 - 7.22 (m, 2H), 7.07 (t, *J* = 7.8Hz, 1H), 4.98

(q, J = 7.8Hz, 1H), 4.65 - 4.52 (m, 1H), 3.19 - 3.03 (m, 2H), 2.42 - 2.27 (m, 1H), 2.20 - 2.06 (m, 2H), 1.82 (d, J = 7.4Hz, 1H), 1.75 - 1.64 (m, 3H), 0.95 (s, 9H).

Example 205. Synthesis of viral protease inhibitor compound 898



Step 1: (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate hydrochloride

[0001614] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (23 g, 55.89 mmol, 1 eq) in HCl/MeOH (4 M, 230 mL, 16.46 eq) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the produce methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (20 g, crude, HCl) as a white solid. MS (ESI) *m/z* 312.1 $[M+H]^+$.

Step 2: (S)-methyl 2-((S)-2-(7-chloro-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001615] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.8 g, 2.30 mmol, 1 eq, HCl) and 7-chloro-4-methoxy-1H-indole-2-carboxylic acid (622.71 mg, 2.76 mmol, 1.2 eq) in DMF (5 mL) and DCM (20 mL) was added DMAP (842.95 mg, 6.90 mmol, 3 eq) and EDCI (881.79 mg, 4.60 mmol, 2 eq), and then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by the addition of H_2O (100 mL) at 0 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced

pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 5:1 to 0:1) to give the product methyl (2S)-2-[[(2S)-2-[(7-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 1.83 mmol, 79.59% yield, 95% purity) as a yellow solid. MS (ESI) *m/z* 519.2 $[M+H]^+$.

Step 3: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-4-methoxy-1H-indole-2-carboxamide

[0001616] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.9 g, 1.73 mmol, 1 eq) in NH_3/MeOH (7 M, 36.00 mL, 145.32 eq) was stirred at 25 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to afford N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-4-methoxy-1H-indole-2-carboxamide (0.8 g, crude) as a yellow solid. MS (ESI) *m/z* 504.2 $[M+H]^+$.

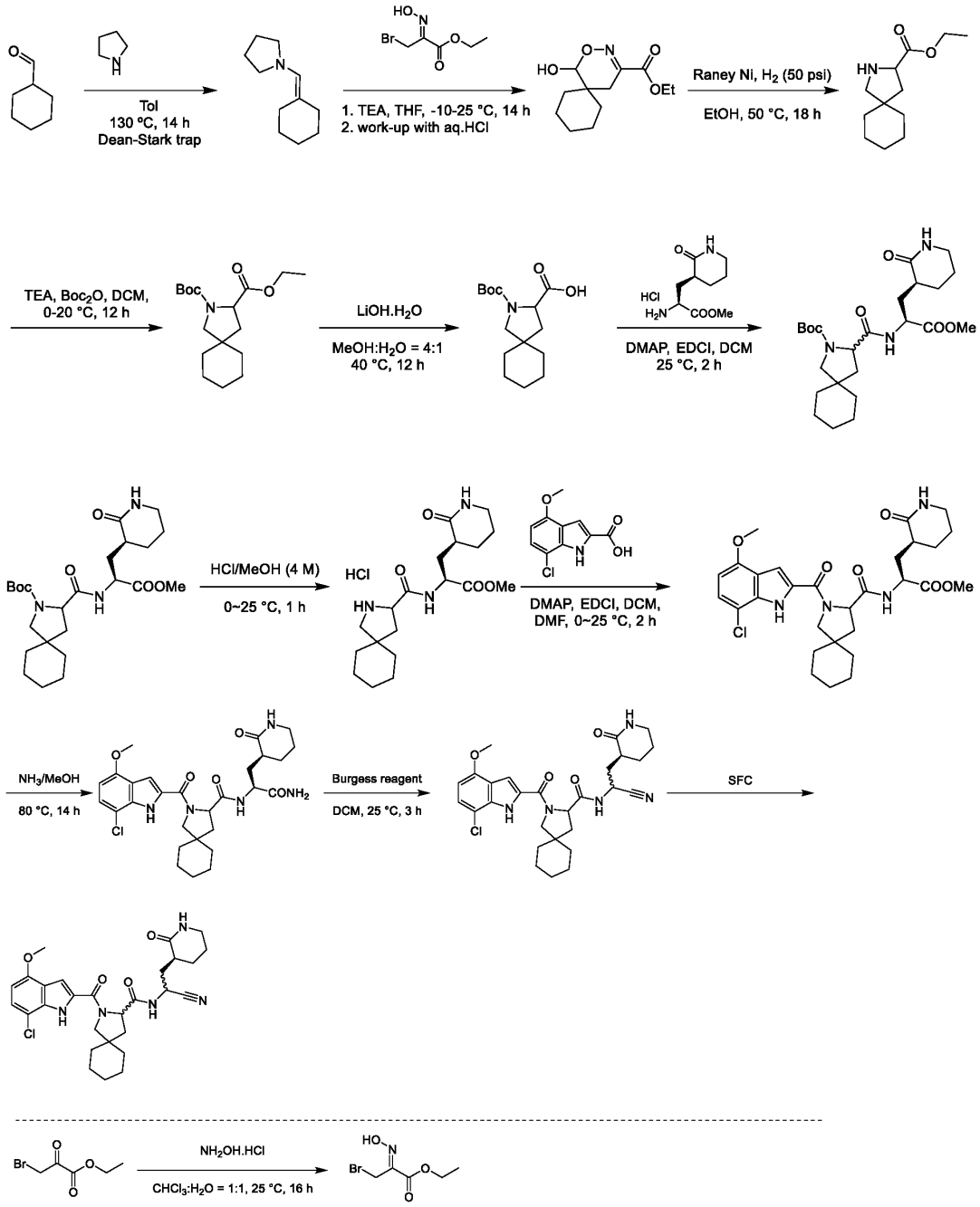
Step 4: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001617] A solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-4-methoxy-1H-indole-2-carboxamide (0.8 g, 1.59 mmol, 1 eq) in DCM (30 mL) was added with Burgess reagent (945.70 mg, 3.97 mmol, 2.5 eq), and then the mixture was stirred at 40 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini C18 250 * 50mm * 10um; mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 28% - 48%, 20min) to give the product 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (0.21 g, 432.13 umol, 27.22% yield, 100% purity) as a white solid. MS (ESI) *m/z* 486.2 $[M+H]^+$.

[0001618] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.70 (br d, *J* = 1.6 Hz, 1H), 8.97 (d, *J* = 7.9 Hz, 1H), 8.65 (d, *J* = 7.5 Hz, 1H), 7.53 (br s, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 5.07 (q, *J* = 7.8 Hz, 1H), 4.56 - 4.43 (m, 1H), 3.89 (s, 3H),

3.15 - 3.02 (m, 2H), 2.30 - 2.22 (m, 2H), 1.87 - 1.68 (m, 4H), 1.59 - 1.39 (br s, 3H), 0.86 - 0.77 (m, 1H), 0.48 - 0.38 (m, 2H), 0.23 - 0.08 (m, 2H)

Example 206. Synthesis of viral protease inhibitor compound 902



Step 1: (Z)-ethyl 3-bromo-2-(hydroxyimino)propanoate

[0001619] To a solution of ethyl 3-bromo-2-oxo-propanoate (60 g, 307.67 mmol, 38.46 mL, 1 eq) in $CHCl_3$ (250 mL) was added $NH_2OH.HCl$ (23.52 g, 338.44 mmol, 1.1 eq) in H_2O (250 mL) under N_2. The mixture was stirred at 25 °C for 16 h. The reaction was quenched by H_2O (500 mL) and then extracted with DCM (300 mL * 4). The combined organic phase was washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a (Z)-ethyl 3-bromo-2-(hydroxyimino)propanoate (51 g, crude) as a yellow solid. MS (ESI) m/z 210.3 $[M+H]^+$.

Step 2: 1-(cyclohexylidenemethyl)pyrrolidine

[0001620] A mixture of cyclohexanecarbaldehyde (15 g, 133.73 mmol, 16.09 mL, 1 eq), pyrrolidine (11.41 g, 160.47 mmol, 13.40 mL, 1.2 eq) in toluene (300 mL) was heated at 130 °C for 14 h and water was removed by Dean-Stark trap. The reaction mixture was concentrated under reduced pressure to give a residue at 50 °C to give 1-(cyclohexylidenemethyl)pyrrolidine (20 g, crude) as a yellow oil. MS (ESI) m/z 166.2 $[M+H]^+$.

Step 3: ethyl 1-hydroxy-2-oxa-3-azaspiro[5.5]undec-3-ene-4-carboxylate

[0001621] To a solution of 1-(cyclohexylidenemethyl)pyrrolidine (20 g, 121.01 mmol, 1 eq) in THF (200 mL) was added a solution of ethyl (2Z)-3-bromo-2-hydroxyimino-propanoate (25.42 g, 121.01 mmol, 1 eq) in THF (200 mL) drop-wise at -10 °C under N_2. After 1 h, TEA (12.24 g, 121.01 mmol, 16.84 mL, 1 eq) was added drop-wise at -10 °C under N_2. The reaction mixture was stirred at 25 °C for 12 h under N_2. The reaction was added with HCl (36%, 2.2 eq, 26 mL in 3.5 vol H_2O) drop-wise at 25 °C, and stirred at 25 °C for 1 h. The reaction mixture was quenched by the addition of H_2O (350 mL) at 25 °C, and extracted with ethyl acetate (200 mL * 3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 1/1) to give a ethyl 1-hydroxy-2-oxa-3-azaspiro[5.5]undec-3-ene-4-carboxylate (15 g, 58.44 mmol, 48.29% yield, 94% purity) as a yellow oil. MS (ESI) m/z 242.2 $[M+H]^+$.

Step 4: ethyl 2-azaspiro[4.5]decane-3-carboxylate

[0001622] To a solution of ethyl 1-hydroxy-2-oxa-3-azaspiro[5.5]undec-3-ene-4-carboxylate (15 g, 62.17 mmol, 1 eq) in EtOH (150 mL) was added Raney Nickel (10.65 g, 124.34 mmol, 2 eq) under Ar_2. The suspension was degassed under vacuum and purged with H_2 (125.58 mg, 62.17 mmol, 1 eq) several times. The mixture was stirred under H_2 (125.58 mg, 62.17 mmol, 1 eq) (50 psi) at 50 °C for 18 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 4/1 to ethyl acetate/methanol = 10/1) to give a ethyl 2-azaspiro[4.5]decane-3-carboxylate (6 g, 22.72 mmol, 36.54% yield, 80% purity) as a yellow and ethyl 2-azaspiro[4.5]decane-3-carboxylate (3 g, 5.11 mmol, 8.22% yield, 36% purity) was obtained as a yellow oil. MS (ESI) m/z 212.2 $[M+H]^+$.

Step 5: 2-tert-butyl 3-ethyl 2-azaspiro[4.5]decane-2,3-dicarboxylate

[0001623] To a solution of ethyl 2-azaspiro[4.5]decane-3-carboxylate (6 g, 28.40 mmol, 1 eq) in DCM (60 mL) was added TEA (5.75 g, 56.79 mmol, 7.90 mL, 2 eq) and Boc_2O (7.44 g, 34.07 mmol, 7.83 mL, 1.2 eq) at 0 °C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was quenched by the addition of H_2O (300 mL), and extracted with ethyl acetate (150 mL * 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 9/1) to give a 2-tert-butyl 3-ethyl 2-azaspiro[4.5]decane-2,3-dicarboxylate (6 g, 19.27 mmol, 67.85% yield, N/A purity) was obtained as a yellow oil. MS (ESI) m/z 312.2 $[M+H]^+$.

Step 6: 2-(tert-butoxycarbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid

[0001624] To a solution of 2-tert-butyl 3-ethyl 2-azaspiro[4.5]decane-2,3-dicarboxylate (7 g, 22.48 mmol, 1 eq) in H_2O (14 mL) and MeOH (56 mL) was added $LiOH.H_2O$ (1.89 g, 44.96 mmol, 2 eq). The mixture was stirred at 40 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (80 mL) and extracted with ethyl acetate.

Step 7: tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate

[0001625] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (6.25 g, 26.40 mmol, 1.1 eq, HCl) and 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (6.8 g, 24.00 mmol, 1 eq) in DCM (90 mL) was added DMAP (5.86 g, 48.00 mmol, 2 eq) and EDCI (6.90 g, 36.00 mmol, 1.5 eq). The mixture was stirred at 25 °C for 2 h. The reaction was quenched by 0.5 M HCl (200 mL) and then extracted with DCM (100 mL * 3). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1 to 0/1) to give a tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (9 g, 18.36 mmol, 76.53% yield, 95% purity) as a white solid. MS (ESI) m/z 466.2 $[M+H]^+$

Step 8: (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate

[0001626] A mixture of tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate (1.5 g, 2.90 mmol, 90% purity, 1 eq) in HCl/MeOH (4 M, 20 mL, 27.59 eq) was cooled to 0 °C, and then stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate (1.5 g, crude, HCl) as a white solid. MS (ESI) m/z 366.1 $[M+H]^+$.

Step 9: (2S)-methyl 2-(2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001627] To a mixture of (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate (1.5 g, 3.55 mmol, 1 eq, HCl) in DCM (30 mL) and DMF (10 mL) was added 7-chloro-4-methoxy-1H-indole-2-carboxylic acid (959.94 mg, 4.25 mmol, 1.2 eq), followed by DMAP (1.30 g, 10.64 mmol, 3 eq) and EDCI (1.36 g, 7.09 mmol, 2 eq) at 0 °C. The resulting mixture was stirred at 25 °C for 2 h. and then the reaction mixture was quenched with water (10 mL) at 0 °C. After extraction with with DCM (10 mL * 3). the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The

residue was purified by column chromatography (SiO_2, DCM:MeOH = 100:1 to 10:1) to give methyl (2S)-2-[[2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.91 g, 3.00 mmol, 84.60% yield, 90% purity) as a yellow oil. MS (ESI) m/z 573.3 $[M+H]^+$.

Step 10: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001628] A mixture of methyl (2S)-2-[[2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.91 g, 3.00 mmol, 90% purity, 1 eq) in NH_3/MeOH (7 M, 17.79 mL, 41.52 eq) was stirred at 80 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.3 g, crude) as a yellow solid. MS (ESI) m/z 558.3 $[M+H]^+$.

Step 11: 2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-N-(1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001629] To a mixture of N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.3 g, 1.98 mmol, 1 eq) in DCM (25 mL) was added Burgess reagent (1.42 g, 5.94 mmol, 3 eq). After stirring at 25 °C for 3 h, the mixture was quenched with water (1 mL) and concentrated under reduced pressure to give a residue (<30 °C). The residue was purified by prep-HPLC (column: Phenomenex Titank C18 Bulk (250 * 100 mm * 10 um); mobile phase:[water(10 mM NH_4HCO_3)-ACN]; B%:40%-75%, 20 min) to give 2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-N-(1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (350 mg, 648.09 umol, 32.73% yield) as a white solid. MS (ESI) m/z 540.1 $[M+H]^+$.

Step 12: 2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-N-(1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001630] 2-(7-Chloro-4-methoxy-1H-indole-2-carbonyl)-N-(1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (350.00 mg, 550.87 umol, 95% purity, 1 eq) was purified by SFC (column:Waters Xbridge BEH C18 (100 * 30 mm * 10 um;mobile phase:[water(10 mM NH_4HCO_3)-ACN]; B%: 35% - 60%, 8 min) to give

2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-N-(1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (62.40 mg, 112.77 umol, 20.47% yield, 97.6% purity) as a white solid. MS (ESI) m/z 540.2 $[M+H]^+$.

[0001631] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.23 - 6.79 (m, 2H), 6.58 - 6.39 (m, 1H), 5.11 (dd, J = 5.7, 10.6 Hz, 1H), 4.77 - 4.52 (m, 1H), 4.03 - 3.76 (m, 4H), 3.74 - 3.37 (m, 1H), 3.47 - 2.89 (m, 2H), 2.65 - 2.10 (m, 3H), 2.09 - 1.27 (m, 16H).

[0001632] 2-(7-Chloro-4-methoxy-1H-indole-2-carbonyl)-N-(1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 2 (131.81 mg, 244.07 umol, 44.31% yield, 100% purity) was obtained as a white solid. MS (ESI) m/z 540.2 $[M+H]^+$.

[0001633] ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.22 - 6.84 (m, 2H), 6.59 - 6.44 (m, 1H), 5.07 - 4.95 (m, 1H), 4.69 - 4.50 (m, 1H), 4.02 - 3.81 (m, 4H), 3.80 - 3.43 (m, 1H), 3.23 - 3.02 (m, 2H), 2.54 - 2.13 (m, 3H), 2.11 - 1.36 (m, 16H).

[0001634] 2-(7-Chloro-4-methoxy-1H-indole-2-carbonyl)-N-(1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 3 (34.64 mg, 64.14 umol, 11.64% yield, 100% purity) was obtained as a white solid. MS (ESI) m/z 540.2 $[M+H]^+$.

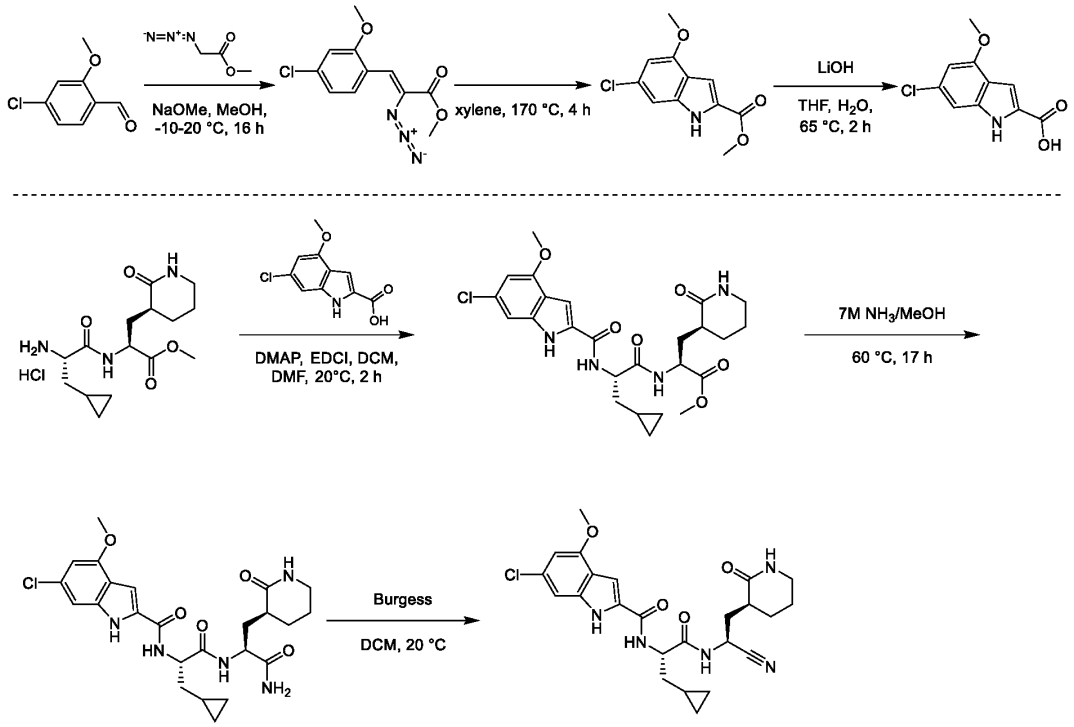
[0001635] 1H NMR (400 MHz, METHANOL-d_4) δ = 7.31 - 6.74 (m, 2H), 6.63 - 6.43 (m, 1H), 5.29 - 4.96 (m, 1H), 4.87 - 4.58 (m, 1H), 3.91 (br d, J = 9.0 Hz, 4H), 3.80 - 3.38 (m, 1H), 3.29 - 3.02 (m, 2H), 2.64 - 2.13 (m, 3H), 2.10 - 1.35 (m, 16H).

[0001636] 2-(7-Chloro-4-methoxy-1H-indole-2-carbonyl)-N-(1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide Isomer 4 (5.66 mg, 10.45 umol, 1.90% yield, 99.7% purity) was obtained as a white solid. MS (ESI) m/z 540.2 $[M+H]^+$.

[0001637] 1H NMR (400 MHz, METHANOL-d_4) δ = 7.31 - 6.77 (m, 2H), 6.62 - 6.46 (m, 1H), 5.17 - 4.91 (m, 1H), 4.75 - 4.56 (m, 1H), 4.04 - 3.80 (m, 4H), 3.73 (d, J = 10.4 Hz, 1H), 3.28 - 3.01 (m, 2H), 2.55 - 2.44 (m, 1H), 2.44 - 2.25 (m, 2H), 2.08 - 1.40 (m, 16H).

[0001638] (50 mL * 2). The aqueous phase were added HCl aq adjust to pH = 2 and extracted with EA (90 mL * 3), The combined organic layers were washed with brine (90 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (6.1 g, crude) was obtained as a white solid. MS (ESI) m/z 284.2 $[M+H]^+$

Example 207. Synthesis of viral protease inhibitor compound 906



Step 1: methyl (Z)-2-azido-3-(4-chloro-2-methoxy-phenyl)prop-2-enoate

[0001639] To a solution of CH_3ONa (2.53 g, 46.90 mmol, 2 *eq*) in MeOH (40 mL) was added a mixture of 4-chloro-2-methoxy-benzaldehyde (4 g, 23.45 mmol, 1 *eq*) and methyl 2-azidoacetate (5.40 g, 46.90 mmol, 2 *eq*) in MeOH (15 mL) at -10 °C. After stirring for 16 h at 20 °C, the solution was diluted with H_2O (60 mL) and concentrated and extracted with ethyl acetate (50 mL*3) and concentrated to give crude. The crude was purified by column (SiO_2, petroleum ether: ethyl acetate=20:1 to 3:1) to give product methyl (Z)-2-azido-3-(4-chloro-2-methoxy-phenyl)prop-2-enoate (3.3 g, 12.33 mmol, 52.58% yield) as a white solid. MS (ESI) *m/z* 268.1 $[M+H]^+$

Step 2: methyl 6-chloro-4-methoxy-1H-indole-2-carboxylate

[0001640] A solution of methyl (Z)-2-azido-3-(4-chloro-2-methoxy-phenyl)prop-2-enoate (3000 mg, 11.21 mmol, 1 *eq*) in xylene (30 mL) was stirred for 4 h at 170 °C. Upon completion, the solution was concentrated to give crude. The crude was purified by column (SiO_2, petroleum ether: ethyl acetate=10:1 to 1:10) to give product methyl 6-chloro-4-methoxy-1H-indole-2-carboxylate (1500 mg, 6.26 mmol, 55.84% yield) as a white solid. MS (ESI) *m/z* 240.1 $[M+H]^+$

Step 3: 6-chloro-4-methoxy-1H-indole-2-carboxylic acid

[0001641] A solution of methyl 6-chloro-4-methoxy-1H-indole-2-carboxylate (1500 mg, 6.26 mmol, 1 *eq*) in THF (15 mL) and H_2O (15 mL) was added with $LiOH.H_2O$ (787.95 mg, 18.78 mmol, 3 *eq*). After stirring for 2 h at 65 °C, the solution was concentrated and extracted with ethyl acetate (50 mL*2) and the water layer was adjusted pH=4-5 with HCl (con) and extracted with ethyl acetate (80 mL*3) and dried over Na_2SO_4 and concentrated to give crude. The crude was used directly for the next step. 6-chloro-4-methoxy-1H-indole-2-carboxylic acid (1070 mg, 4.74 mmol, 75.77% yield) as a brown solid. MS (ESI) *m/z* 226.2 $[M+H]^+$

Step 4: methyl (2S)-2-[[(2S)-2-[(6-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001642] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 1.44 mmol, 1 *eq*, HCl) in DCM (10 mL) and DMF (10 mL) was added DMAP (351.22 mg, 2.87 mmol, 2 *eq*), 6-chloro-4-methoxy-1H-indole-2-carboxylic acid (372.98 mg, 1.65 mmol, 1.15 *eq*) and EDCI (551.13 mg, 2.87 mmol, 2 *eq*). After stirring for 2 h at 20 °C, the mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (50mL *3) and concentrated to give crude. The crude was purified by column (SiO_2, petroleum ether: ethyl acetate=10:1 to EA: MeOH=10:1) to give methyl (2S)-2-[[(2S)-2-[(6-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 963.41 umol, 67.02% yield) as a white solid. MS (ESI) *m/z* 519.3 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-4-methoxy-1H-indole-2-carboxamide

[0001643] A solution of methyl (2S)-2-[[(2S)-2-[(6-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 963.41 umol, 1 *eq*) in NH_3/MeOH (7 M, 20 mL, 145.32 *eq*) was stirred for 17 h at 60 °C. The solution was concentrated to afford N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-4-methoxy-1H-indole-2-carboxamide (485 mg, crude) as a white solid. The crude was used directly for the next step. MS (ESI) *m/z* 504.3 $[M+H]^+$

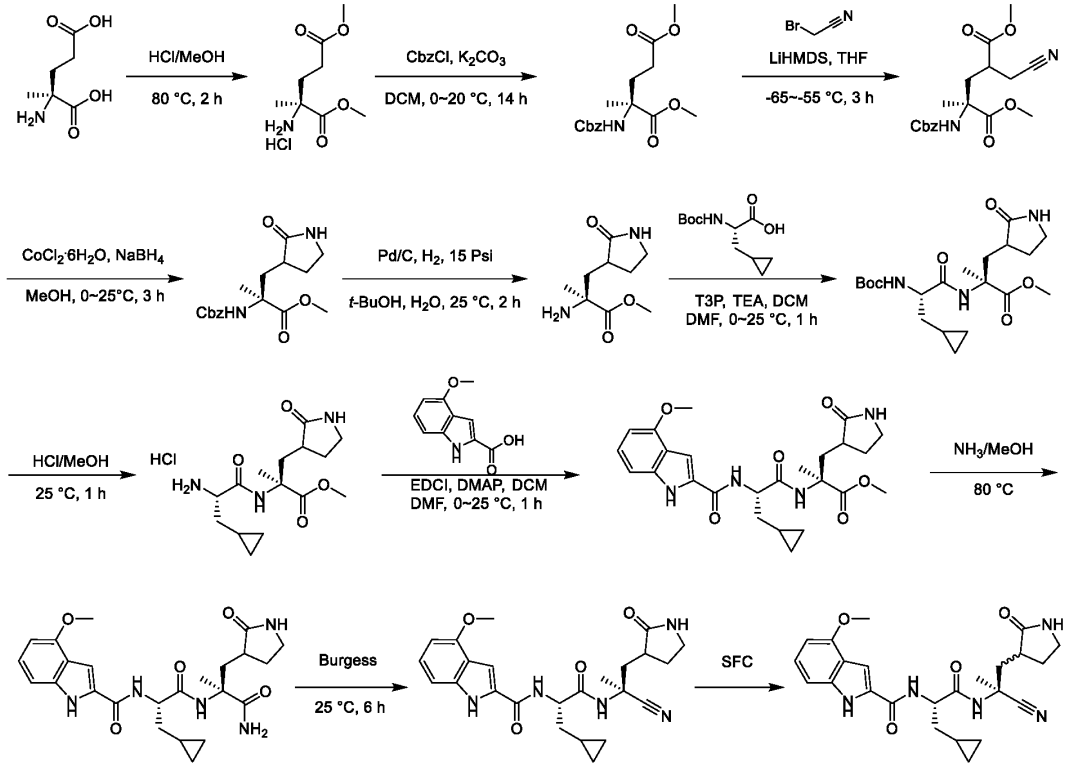
Step 6: 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[0001644] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-4-methoxy-1H-indole-2-carboxamide (470 mg, 932.58 umol, 1 *eq*) in DCM (25 mL) was added Burgess reagent (666.72 mg, 2.80 mmol, 3 *eq*). After stirring for 3 h at 20 °C, the solution was washed with brine (50 mL) and dried with using N_2 to give a crude. The crude was purified by pre-HPLC(neutral) to afford 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (210 mg, 432.13 umol, 46.34% yield) as a white solid. MS (ESI) *m/z* 486.3 $[M+H]^+$

[0001645] Pre-HPLC condition: column: Waters Xbridge C18 150*50mm* 10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 30%-60%,10min

[0001646] ^1H NMR (400MHz, DMSO-d_6) δ = 11.72 (s, 1H), 8.91 (br d, *J*=8.2 Hz, 1H), 8.58 (br d, *J*=7.3 Hz, 1H), 7.53 (br s, 1H), 7.38 (s, 1H), 7.03 (s, 1H), 6.56 (s, 1H), 5.17 - 4.93 (m, 1H), 4.53 - 4.31 (m, 1H), 3.91 (s, 3H), 3.09 (br s, 2H), 2.37 - 2.15 (m, 2H), 1.89 - 1.27 (m, 7H), 0.80 (br s, 1H), 0.40 (br s, 1H), 0.23 - 0.10 (m, 2H).

Example 208. Synthesis of viral protease inhibitor compound 1511



Step 1: (S)-dimethyl 2-amino-2-methylpentanedioate

[0001647] A mixture of (2S)-2-amino-2-methyl-pentanedioic acid (1 g, 6.21 mmol, 1 *eq*) in HCl/MeOH (4 M, 10 mL, 6.45 *eq*) was stirred at 80 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (S)-dimethyl 2-amino-2-methylpentanedioate (1.4 g, crude) as a yellow oil. MS (ESI) m/z 190.2 $[M+H]^+$.

Step 2: (S)-dimethyl 2-(((benzyloxy)carbonyl)amino)-2-methylpentanedioate

[0001648] To a mixture of (S)-dimethyl 2-amino-2-methylpentanedioate (1.1 g, 4.87 mmol, 1 eq, HCl) in DCM (11 mL) was added K_2CO_3 (2.02 g, 14.62 mmol, 3 eq) and CbzCl (914.69 mg, 5.36 mmol, 762.24 uL, 1.1 eq) at 0 °C. After stirring at 20 °C for 14 h, the reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 10:1 to 2:1) to give (S)-dimethyl 2-(((benzyloxy)carbonyl)amino)-2-methylpentanedioate (920 mg, 2.85 mmol, 58.37% yield) as a yellow oil. MS (ESI) m/z 324.1 $[M+H]^+$.

Step 3: (2S)-dimethyl 2-(((benzyloxy)carbonyl)amino)-4-(cyanomethyl)-2-methylpentanedioate

[0001649] To a mixture of (S)-dimethyl 2-(((benzyloxy)carbonyl)amino)-2-methylpentanedioate (920 mg, 2.42 mmol, 85% purity, 1 eq) in anhydrous THF (18.4 mL) was added LiHMDS (1 M, 5.32 mL, 2.2 eq) drop-wise under N_2 atmosphere at -65~-55 °C for 0.5 h. After a further 1 h of stirring at -65~-55 °C, 2-bromoacetonitrile (435.14 mg, 3.63 mmol, 241.75 uL, 1.5 eq) was added drop-wise to the mixture solution over a period of 0.5 h while maintaining the temperature under -65~-55 °C. The reaction mixture was stirred at -65~-55 °C for 1 h under N_2. Upon completion, the reaction mixture was quenched with pre-cooled (dry-ice in EtOH) MeOH (2.8 mL) and a pre-cooled (dry-ice in EtOH) acetic acid in THF solution (0.46mL HOAc/3.7 mL THF) in order at -60 °C. After further 30 min of stirring at -60 °C, the cooling bath was removed and replaced with water bath. The reaction mixture was allowed to warm up to 0 ± 5 °C and then concentrated under reduced pressure at 30 °C to give a black brown solid. The obtained residue was dissolved in ethyl acetate (37 mL), washed with brine (18 mL * 2). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 10:1 to 2:1) to give (2S)-dimethyl 2-(((benzyloxy)carbonyl)amino)-4-(cyanomethyl)-2-methylpentanedioate (740 mg, 1.84 mmol, 75.99% yield, 90% purity) as a yellow oil. MS (ESI) m/z 363.1 $[M+H]^+$.

Step 4: (2S)-methyl 2-(((benzyloxy)carbonyl)amino)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate

[0001650] To a stirred solution of (2S)-dimethyl 2-(((benzyloxy)carbonyl)amino)-4-(cyanomethyl)-2-methylpentanedioate (740 mg, 1.84 mmol, 90% purity, 1 eq) in MeOH (34 mL) was added $CoCl_2.6H_2O$ (262.37 mg, 1.10 mmol, 0.6 eq) at 0 °C, and then $NaBH_4$ (419 mg, 11.08 mmol, 6.03 eq) was added into the mixture in 4 batches at 0 °C for 1 h, and then the black mixture was stirred at 25 °C for 2 h. Upon completion, the mixture was quenched with NH_4Cl aq. (41 mL) at 0 °C, the mixture was filtered through celite, then extracted with DCM (41 mL * 3), the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to get the crude product. The residue was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 10:1 to 1:1) to give (2S)-methyl 2-(((benzyloxy)carbonyl)amino)-2-methyl-3-(2-oxopyrrolidin-3-

yl)propanoate (320 mg, 957.03 umol, 52.07% yield) as a white solid. MS (ESI) m/z 335.2 $[M+H]^+$.

Step 5: (2S)-methyl 2-amino-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate

[0001651] To a mixture of (2S)-methyl 2-(((benzyloxy)carbonyl)amino)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (320 mg, 957.03 umol, 1 eq) in H_2O (1.5 mL) and t-BuOH (6 mL) under N_2 was added Pd/C (160 mg, 10% purity). The resulting mixture was degassed and purged with H_2 for 3 times, and then the mixture was stirred under H_2 (15 Psi) at 25 °C for 2 h. Upon completion, the mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give (2S)-methyl 2-amino-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (140 mg, crude) as a white solid. MS (ESI) m/z 201.1 $[M+H]^+$.

Step 6: (2S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpropanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate

[0001652] To a solution of (2S)-methyl 2-amino-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (140 mg, 699.18 umol, 1 eq) in DCM (2 mL) and DMF (1 mL) was added (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (192.36 mg, 839.02 umol, 1.2 eq), TEA (212.25 mg, 2.10 mmol, 291.95 uL, 3 eq). After the addion of T_3P (667.40 mg, 1.05 mmol, 623.74 uL, 50% purity, 1.5 eq) at 0 °C, the mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give (2S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpropanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (280 mg, 612.41 umol, 87.59% yield, 90% purity) as yellow oil. MS (ESI) m/z 412.3 $[M+H]^+$.

Step 7: (2S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate

[0001653] A solution of (2S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpropanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (260 mg, 568.66 umol, 90% purity, 1 eq) in HCl/MeOH (4 M, 2.6 mL, 18.29 eq) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to

give (2S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (200 mg, crude, HCl) as yellow solid. MS (ESI) m/z 312.2 $[M+H]^+$.

Step 8: (2S)-methyl 2-((S)-3-cyclopropyl-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate

[0001654] To a solution of (2S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (200 mg, 546.23 umol, 95% purity, 1 eq, HCl) in DCM (4 mL) and DMF (2 mL) was added 4-methoxy-1H-indole-2-carboxylic acid (125.32 mg, 655.48 umol, 1.2 eq), DMAP (200.20 mg, 1.64 mmol, 3 eq), and EDCI (209.43 mg, 1.09 mmol, 2 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h, and then the reaction mixture was diluted with water (20 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give (2S)-methyl 2-((S)-3-cyclopropyl-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (300 mg, 451.97 umol, 82.74% yield, 73% purity) as a yellow oil. MS (ESI) m/z 485.3 $[M+H]^+$.

Step 9: N-((2S)-1-(((2S)-1-amino-2-methyl-1-oxo-3-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001655] A solution of (2S)-methyl 2-((S)-3-cyclopropyl-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-2-methyl-3-(2-oxopyrrolidin-3-yl)propanoate (280.00 mg, 421.84 umol, 73% purity, 1 eq) in NH_3/MeOH (7 M, 6 mL, 99.56 eq) was stirred at 80 °C for 86 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give N-((2S)-1-(((2S)-1-amino-2-methyl-1-oxo-3-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (35 mg, 70.82 umol, 16.79% yield, 95% purity) as a yellow solid. MS (ESI) m/z 470.3 $[M+H]^+$.

Step 10: N-((2S)-1-(((2S)-2-cyano-1-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001656] To a solution of N-((2S)-1-(((2S)-1-amino-2-methyl-1-oxo-3-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (30 mg, 60.70 umol, 95% purity, 1 eq) in DCM (1 mL) was added Burgess reagent (43.40 mg, 182.10 umol, 3 eq), and then was stirred at 25 °C for 6 h. Upon completion, the reaction mixture was quenched by addition H_2O (0.1 mL) at 20 °C and then concentrated under reduced pressure (< 20 °C) to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100* 25mm* 5um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 20%-50%, 10 min) to give N-((2S)-1-(((2S)-2-cyano-1-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (25 mg, 52.60 umol, 86.66% yield, 95% purity) as a white solid. MS (ESI) m/z 452.2 $[M+H]^+$.

Step 11: N-((2S)-1-(((2S)-2-cyano-1-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

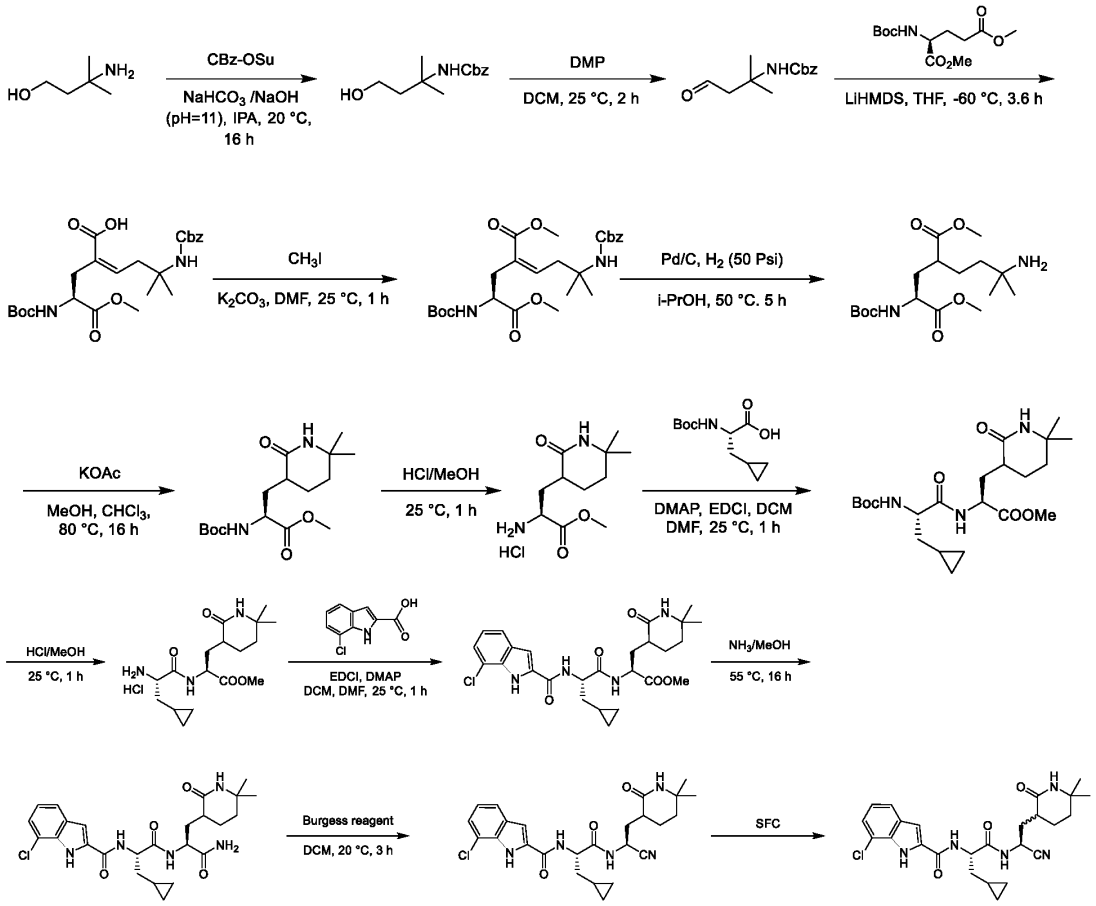
[0001657] N-((2S)-1-(((2S)-2-cyano-1-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (25 mg, 52.60 umol, 95% purity, 1 eq) was purified by SFC (column: DAICEL CHIRALPAK AD(250 mm* 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O IPA]; B%: 50%-50%, 7 min) to give N-((2S)-1-(((2S)-2-cyano-1-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide Isomer 1 (2.35 mg, 5.10 umol, 9.69% yield, 97.9% purity) as a white solid. MS (ESI) m/z 452.1 $[M+H]^+$.

[0001658] ^1H NMR (400MHz, MeOD-d_4) δ = 7.26 (d, J=0.7 Hz, 1H), 7.19 - 7.11 (m, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 4.59 (t, J = 7.3 Hz, 1H), 3.93 (s, 3H), 3.38 - 3.32 (m, 2H), 2.77 - 2.66 (m, 1H), 2.54 - 2.45 (m, 1H), 2.40 (dd, J = 5.1, 14.3 Hz, 1H), 2.07 (dd, J = 7.3, 14.3 Hz, 1H), 2.02 - 1.91 (m, 1H), 1.86 (td, J = 7.1, 14.0 Hz, 1H), 1.74 (s, 3H), 1.68 (td, J = 7.1, 14.1 Hz, 1H), 0.93 - 0.79 (m, 1H), 0.59 - 0.44 (m, 2H), 0.26 - 0.14 (m, 2H).

[0001659] N-((2S)-1-(((2S)-2-cyano-1-(2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide Isomer 2 (2.08 mg, 4.53 umol, 8.62% yield, 98.4% purity) was obtained as a white solid. MS (ESI) m/z 452.1 $[M+H]^+$.

[0001660] ^{1}H NMR (400MHz, MeOD-d_4) δ = 7.26 (s, 1H), 7.20 - 7.13 (m, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.52 (d, J = 7.7 Hz, 1H), 4.62 (dd, J = 6.4, 7.9 Hz, 1H), 3.93 (s, 3H), 3.28 - 3.16 (m, 2H), 2.73 - 2.61 (m, 1H), 2.39 (td, J = 6.6, 12.8 Hz, 1H), 2.27 (dd, J = 7.4, 14.9 Hz, 1H), 2.01 - 1.92 (m, 1H), 1.92 - 1.78 (m, 2H), 1.76 - 1.66 (m, 4H), 0.89 - 0.78 (m, 1H), 0.55 - 0.44 (m, 2H), 0.24 - 0.14 (m, 2H)

Example 209. Synthesis of viral protease inhibitor compound 749



Step 1: benzyl N-(3-hydroxy-1,1-dimethyl-propyl)carbamate

[0001661] To a solution of 3-amino-3-methyl-butan-1-ol (3.5 g, 33.93 mmol, 1 eq) in IPA (60 mL) was added 60 mL of saturated $NaHCO_3$ (64.80 g, 771.37 mmol, 30 mL, 22.74 eq), which is a pH=11 buffer, adjusted with 4 M NaOH (4 M, 30 mL, 3.54 eq). The reaction mixture was cooled to 0 °C, and then benzyl 2,5 -dioxopyrrolidine-1-carboxylate (7.91 g, 33.93 mmol, 1 eq) was added. The reaction mixture was stirred at 20 °C for 16 h.

Upon completion, the reaction mixture was filtered and then concentrated under reduced pressure to remove IPA. The residue was diluted with H_2O (50 mL) and extracted with ethyl acetate (50 mL * 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 5/1) to afford benzyl N-(3-hydroxy-1,1-dimethyl-propyl)carbamate (5 g, 20.02 mmol, 59.00% yield, 95% purity) as a colorless oil. MS (ESI) *m/z* 238.1 $[M+H]^+$

Step 2: benzyl N-(1,1-dimethyl-3-oxo-propyl)carbamate

[0001662] To a solution of benzyl N-(3-hydroxy-1,1-dimethyl-propyl)carbamate (2.2 g, 9.27 mmol, 1 eq) in DCM (1 mL) was added DMP (4.72 g, 11.13 mmol, 3.44 mL, 1.2 eq). The reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL * 2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 20/1 to 10/1) to afford N-(1,1-dimethyl-3-oxo-propyl)carbamate (1.2 g, 4.59 mmol, 49.51% yield, 90% purity) as a colorless oil. MS (ESI) *m/z* 236.1 $[M+H]^+$

Step 3: (Z)-5-(benzyloxycarbonylamino)-2-[(2S)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxo-propyl]-5-methyl-hex-2-enoic acid

[0001663] To a solution of dimethyl (2S)-2-(tert-butoxycarbonylamino)pentanedioate (1.4 g, 5.09 mmol, 1 eq) in THF (15 mL) was added a solution of LiHMDS (1 M, 10.68 mL, 2.1 eq) drop-wise at -60 °C under N_2. After stirring at -60 °C for 0.5 h, benzyl N-(1,1-dimethyl-3-oxo-propyl)carbamate (1.20 g, 5.09 mmol, 1 eq) in THF (10 mL) was added at below -60 °C and the reaction mixture was stirred at -60 °C for 3 h. Upon completion, the reaction mixture was quenched by addition AcOH 5 mL in THF (20 mL) at 0 °C and concentrated under reduced pressure to give a residue. The residue was purified by neutral prep-HPLC (column: Welch Xtimate C18 250*70mm#10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 20%-50%,20min) to get (Z)-5-(benzyloxycarbonylamino)-2-[(2S)-2-(tert-butoxycarbonylamino)-3-methoxy-3- oxo-propyl]-5-methyl-hex-2-enoic acid (230 mg, 456.60 umol, 8.98% yield, 95% purity) as a white solid. MS (ESI) *m/z* 379.1 $[M+H-100]^+$

Step 4: dimethyl (2Z,4S)-2-[3-(benzyloxycarbonylamino)-3-methyl-butylidene]-4-(tert-butoxycarbony l mino)pentanedioate

[0001664] To a mixture of (Z)-5-(benzyloxycarbonylamino)-2-[(2S)-2-(tert-butoxycarbonylamino)-3-methoxy -3-oxo-propyl]-5-methyl-hex-2-enoic acid (250 mg, 522.43 umol, 1 eq) in DMF (2.5 mL) was added K_2CO_3 (144.41 mg, 1.04 mmol, 2 eq) and CH_3I (222.46 mg, 1.57 mmol, 97.57 uL, 3 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was quenched by the addition of H_2O (10 mL) at 0 °C, and then diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue compound dimethyl (2Z,4S)-2-[3- (benzyloxycarbonylamino)-3-methyl-butylidene]-4-(tert-butoxycarbonylamino)pentanedioate (230 mg, 420.25 umol, 80.44% yield, 90% purity) as a colorless oil. The residue was used next step directly. MS (ESI) *m/z* 393.2 $[M+H-100]^+$

Step 5: dimethyl (4S)-2-(3-amino-3-methyl-butyl)-4-(tert-butoxy carbonylamino)pentanedioate

[0001665] To a mixture of dimethyl (2Z,4S)-2-[3-(benzyloxycarbonylamino)-3-methyl-butylidene]-4-(tert- butoxycarbonylamino)pentanedioate (230 mg, 466.95 umol, 1 eq) in i-PrOH (10 mL) was added Pd/C (300 mg, 466.95 umol, 10% purity, 1 eq). The mixture was stirred at 50 °C for 5 h under H_2 (50 Psi). Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue compound dimethyl (4S)-2-(3-amino-3-methyl-butyl)-4-(tert-butoxycarbonylamino) pentanedioate (120 mg, 299.63 umol, 64.17% yield, 90% purity) as a colorless oil and used directly next step. MS (ESI) *m/z* 361.2 $[M+H]^+$

Step 6: methyl (2S)-2-(tert-butoxycarbonylamino)-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate

[0001666] To a mixture of dimethyl (4S)-2-(3-amino-3-methyl-butyl)-4-(tert-butoxycarbonylamino) pentanedioate (120 mg, 332.92 umol, 1 eq) in MeOH (0.5 mL) and $CHCl_3$ (0.05 mL) was added KOAc (65.35 mg, 665.84 umol, 2 eq). The mixture was stirred at 80 °C for 16 h. Upon completion, the residue was diluted with H_2O 5 mL and extracted with ethyl acetate (5 mL * 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to

give a residue compound methyl (2S)-2-(tert-butoxycarbonylamino)-3-(6,6- dimethyl-2-oxo-3-piperidyl)propanoate (100 mg, 274.05 umol, 82.32% yield, 90% purity) as a colorless oil and used directly. MS (ESI) *m/z* 329.2 $[M+H]^+$

Step 7: methyl (2S)-2-amino-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate

[0001667] Methyl (2S)-2-(tert-butoxycarbonylamino)-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (100 mg, 304.50 umol, 1 eq) was added with HCl/MeOH (4 M, 76.13 uL, 1 eq). The resulting mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue compound methyl (2S)-2-amino-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (80 mg, 287.07 umol, 94.27% yield, 95% purity, HCl) as a colorless oil.

Step 8: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(6,6- dimethyl-2-oxo-3-piperidyl)propanoate

[0001668] To a mixture of methyl (2S)-2-amino-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (80 mg, 302.17 umol, 1 eq, HCl) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (69.28 mg, 302.17 umol, 1 eq) in DCM (2 mL) and DMF (1 mL) was added DMAP (73.83 mg, 604.35 umol, 2 eq) and EDCI (115.85 mg, 604.35 umol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL * 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 3/1) to afford methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (110 mg, 225.23 umol, 74.54% yield, 90% purity) as a colorless oil. MS (ESI) *m/z* 440.3 $[M+H]^+$

Step 9: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(6,6-dimethyl-2-oxo-3- piperidyl)propanoate

[0001669] Methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(6,6- dimethyl-2-oxo-3-piperidyl)propanoate (110 mg, 250.26 umol, 1 eq) was added with HCl/MeOH (4 M, 7.33 mL, 117.21 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue compound methyl (2S)-2-[[(2S)-2-amino-3- cyclopropyl-

propanoyl]amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (90 mg, 239.43 umol, 95.67% yield, HCl) as a colorless oil.

Step 10: methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate

[0001670] To a mixture of 7-chloro-1H-indole-2-carboxylic acid (46.83 mg, 239.43 umol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (90 mg, 239.43 umol, 1 *eq*, HCl) in DCM (4 mL) and DMF (2 mL) was added EDCI (91.80 mg, 478.86 umol, 2 *eq*) and DMAP (58.50 mg, 478.86 umol, 2 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O 20 mL and extracted with EA 40 mL (20 mL * 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether: ethyl acetate = 0:1) to get the compound methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl) amino]-3-cyclopropyl-propanoyl]amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (100 mg, 183.75 umol, 76.74% yield, 95% purity) as a white solid. MS (ESI) *m/z* 517.3 $[M+H]^+$

Step 11: N-[(1S)-2-[[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide

[0001671] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (100 mg, 193.42 umol, 1 eq) in NH_3/MeOH (7 M, 10.00 mL, 361.91 eq) was stirred at 55 °C for another 16 h. Upon completion, the reaction mixture concentrated under reduced pressure to give a residue and used next step directly. Compound N-[(1S)-2-[[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (100 mg, 185.26 umol, 95.78% yield, 93% purity) was obtained as a white solid. MS (ESI) *m/z* 502.2 $[M+H]^+$

Step 12: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001672] To a mixture of N-[(1S)-2-[[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (80 mg, 159.36 umol, 1 eq) in DCM (5 mL) was added Burgess

reagent (75.95 mg, 318.72 umol, 2 eq). The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was diluted with H_2O (5 mL) and extracted with DCM (5 mL * 2). The combined organic layers were concentrated with using blow-dry to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min) to give the mixture product (65 mg) as a white solid. The white solid (65 mg) was separated by SFC (column: REGIS (s,s) WHELK-O1 (250mm*30mm,5um);mobile phase: [0.1%NH_3H_2O IPA];B%: 55%-55%,8 min) to get the compound 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (35 mg, 72.32 umol, 45.38% yield, 100% purity) and 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (25 mg, 51.65 umol, 32.41% yield, 100% purity) as a white solid. MS (ESI) *m/z* 484.2 $[M+H]^+$

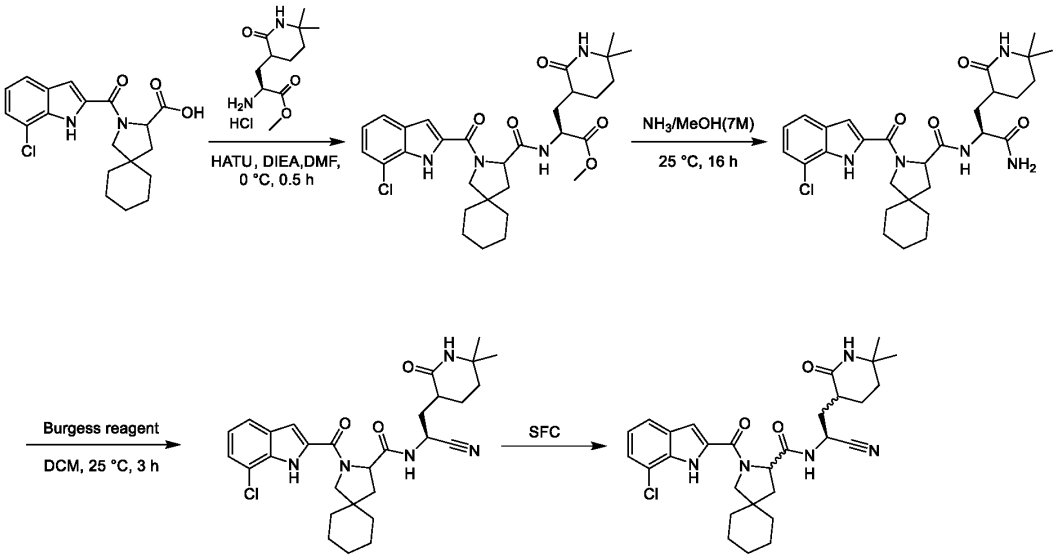
Isomer 1:

[0001673] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.86 - 11.59 (m, 1H), 9.00 (d, *J*=8.0 Hz, 1H), 8.72 (d, *J*=7.6 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.49 (s, 1H), 7.31 (d, *J*=7.5 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.07 (t, *J*=7.8 Hz, 1H), 5.09 (q, *J*=8.0 Hz, 1H), 4.61 - 4.46 (m, 1H), 2.30 - 2.08 (m, 2H), 1.88 - 1.67 (m, 3H), 1.64 - 1.38 (m, 4H), 1.17 - 1.03 (m, 6H), 0.89 - 0.70 (m, 1H), 0.51 - 0.36 (m, 2H), 0.28 - 0.01 (m, 2H).

Isomer 2:

[0001674] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.73 (s, 1H), 9.04 (d, *J*=7.4 Hz, 1H), 8.74 (d, *J*=7.7 Hz, 1H), 7.63 (d, *J*=7.9 Hz, 1H), 7.51 (s, 1H), 7.31 (d, *J*=7.5 Hz, 1H), 7.26 (s, 1H), 7.07 (t, *J*=7.7 Hz, 1H), 5.02 (q, *J*=7.4 Hz, 1H), 4.61 - 4.52 (m, 1H), 2.32 (td, *J*=6.8, 13.7 Hz, 1H), 2.20 - 2.06 (m, 1H), 1.88 - 1.49 (m, 7H), 1.12 (d, *J*=8.0 Hz, 6H), 0.88 - 0.70 (m, 1H), 0.52 - 0.34 (m, 2H), 0.26 - 0.05 (m, 2H).

Example 210. Synthesis of viral protease inhibitor compound 928



[0001675] Step 1: methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate

[0001676] To a mixture of 2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (354.36 mg, 982.06 umol, 1 eq) and methyl (2S)-2-amino-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (260 mg, 982.06 umol, 1 eq, HCl) in DMF (10 mL) was added HATU (448.09 mg, 1.18 mmol, 1.2 eq), DIEA (380.78 mg, 2.95 mmol, 513.17 uL, 3 eq) in DMF (5 mL) was added at 0 °C.The mixture was stirred at 0 °C for 30 min. Upon completion, the reaction mixture was diluted with H_2O 50 mL and extracted with EA 100 mL (50 mL * 2). The combined organic layers were washed with brine 50 mL (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=10/1 to 0/1) to get the compound methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl] amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (550 mg, 866.74 umol, 88.26% yield, 90% purity) as a white solid. MS (ESI) m/z 571.3 $[M+H]^+$

[0001677] Step 2: N-[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-oxo-ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001678] To a mixture of methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3- carbonyl]amino]-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate

(550 mg, 963.04 umol, 1 eq) was added NH_3/MeOH (7 M, 137.58 uL, 1 eq) at 25 °C. The mixture was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue compound N-[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-oxo-ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (520 mg, 841.58 umol, 87.39% yield, 90% purity) as a white solid and the residue was used next step directly. MS (ESI) m/z 556.3 $[M+H]^+$

[0001679] Step 3: 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[0001680] To a mixture of N-[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-oxo-ethyl]-2- (7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (500 mg, 899.13 umol, 1 eq) in DCM (10 mL) was added BURGESS REAGENT (428.53 mg, 1.80 mmol, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was diluted with H_2O 10 mL and extracted with DCM 20 mL (10 mL * 2). The combined organic layers were washed with brine 10 mL (10 mL * 1) and blow-drying by N2 to give a residue. The residue was purified by neutral prep-HPLC (column: Waters Xbridge C18 150*50mm* 10um; mobile phase: [water(10mM NH4HCO3)-ACN];B%: 40%-60%,10min). MS (ESI) m/z 538.2 $[M+H]^+$

[0001681] Isomer 1&2:

[0001682] 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (100 mg, 185.10 umol, 20.59% yield, 99.6% purity) was obtained as a white solid.

[0001683] ^1H NMR (400MHz, DMSO-d6) δ = 11.10 (br s, 1H), 8.70 (br d, J=16.5 Hz, 1H), 7.62 (br s, 1H), 7.38 - 6.82 (m, 4H), 4.98 (br s, 1H), 4.60 (br s, 1H), 3.83 (br d, J=10.1 Hz, 1H), 3.62 (br s, 1H), 2.31 - 1.96 (m, 3H), 1.94 - 1.26 (m, 16H), 1.22 - 1.01 (m, 6H)

[0001684] Isomer 3:

[0001685] 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (50 mg, 92.92 umol, 10.33% yield, 100% purity) was obtained as a white solid.

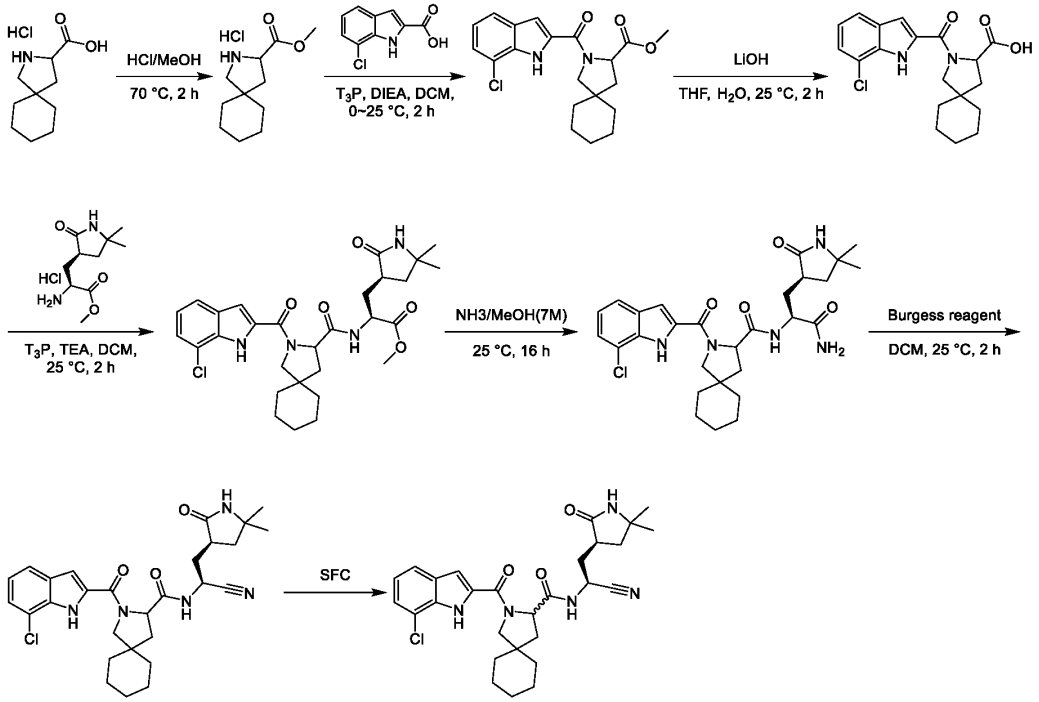
[0001686] ^{1}H NMR (400MHz, DMSO-d6) δ = 11.12 (br s, 1H), 9.01 - 8.62 (m, 1H), 7.83 - 7.52 (m, 1H), 7.49 - 6.65 (m, 4H), 4.94 (br d, J=5.7 Hz, 1H), 4.61 (br s, 1H), 4.00 - 3.33 (m, 2H), 2.35 - 1.99 (m, 3H), 1.91 - 1.28 (m, 16H), 1.20 - 1.07 (m, 6H)

[0001687] Isomer 4:

[0001688] 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (50 mg, 90.69 umol, 10.09% yield, 97.6% purity) was obtained as a white solid.

[0001689] ^{1}H NMR (400MHz, DMSO-*d*6) δ = 11.54 - 10.62 (m, 1H), 8.96 - 8.58 (m, 1H), 7.63 (br d, *J*=7.3 Hz, 1H), 7.39 - 6.91 (m, 4H), 4.94 (q, *J*=6.8 Hz, 1H), 4.60 (br s, 1H), 3.92 - 3.46 (m, 2H), 2.31 - 2.01 (m, 3H), 1.76 - 1.29 (m, 16H), 1.14 (d, *J*=18.3 Hz, 6H)

Example 211. Synthesis of viral protease inhibitor compound 930



Step 1: methyl 2-azaspiro[4.5]decane-3-carboxylate

[0001690] A mixture of 2-azaspiro[4.5]decane-3-carboxylic acid (400 mg, 1.82 mmol, 1 *eq*, HCl) in HCl/MeOH (4 M, 6 mL, 13.18 *eq*) was stirred at 70 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl 2-azaspiro[4.5]decane-3-carboxylate (400 mg, 1.71 mmol, 94.00% yield, HCl) as a white solid. MS (ESI) *m/z* 198.2 $[M+H]^+$.

Step 2: methyl 2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate

[0001691] To a mixture of methyl 2-azaspiro[4.5]decane-3-carboxylate (400 mg, 1.71 mmol, 1 *eq*, HCl) and 7-chloro-1H-indole-2-carboxylic acid (334.74 mg, 1.71 mmol, 1 *eq*) in DCM (6 mL) was added DIEA (663.54 mg, 5.13 mmol, 894.26 uL, 3 *eq*) and T_3P (816.78 mg, 2.57 mmol, 763.34 uL, 1.5 *eq*) in one portion at 0 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-TLC (SiO_2, petroleum ether**:** ethyl acetate = 0:1) to give methyl 2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate (350 mg, 933.68 umol, 54.56% yield) as a white solid. MS (ESI) *m/z* 375.1 $[M+H]^+$

Step 3: 2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid

[0001692] A mixture of methyl 2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylate (350 mg, 933.68 umol, 1 *eq*) in THF (2 mL) and H_2O (2 mL) was added $LiOH.H_2O$ (78.36 mg, 1.87 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was adjusted to acidity by 1M HCl and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (15 mL * 1), dried over Na_2SO_4, and filtered and concentrated under reduced pressure to give 2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (280 mg, 775.98 umol, 83.11% yield) as a white solid. MS (ESI) *m/z* 361.0 $[M+H]^+$

Step 4: methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[0001693] To a mixture of 2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (250 mg, 692.84 umol, 1 *eq*) and methyl (2S)-2-amino-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (225.82 mg, 900.69 umol, 1.3 *eq*, HCl) in

DCM (4 mL) was added T_3P (661.35 mg, 1.04 mmol, 618.08 uL, 50% purity, 1.5 *eq*) and TEA (210.32 mg, 2.08 mmol, 289.30 uL, 3 *eq*) in one portion at 0 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-TLC (SiO2, PE: ethyl acetate = 0: 1) to give methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (270 mg, 484.67 umol, 69.95% yield) as a white solid. MS (ESI) *m/z* 557.1 $[M+H]^+$

Step 5: N-[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo-ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001694] A mixture of methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (250 mg, 448.77 umol, 1 *eq*) in NH_3/MeOH(7 M, 5 mL, 77.99 *eq*) was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo-ethyl]-2- (7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (240 mg, 442.75 umol, 98.66% yield) as a white solid. MS (ESI) *m/z* 542.2 $[M+H]^+$

Step 6: 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[0001695] A mixture of N-[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo-ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (250 mg, 392.02 umol, 85% purity, 1 *eq*) in DCM (5 mL) was added Burgess reagent (186.84 mg, 784.03 umol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 35%-65%,8min) to give 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (100 mg, 190.82 umol, 48.68% yield) as a white solid. MS (ESI) *m/z* 524.2 $[M+H]^+$

Step 7: 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[0001696] The white solid was separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 55%-55%,10min) to give 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (2 mg, 3.82 umol, 2.00% yield), 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (2 mg, 3.82 umol, 2.00% yield), 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (30 mg, 57.25 umol, 30.00% yield), 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (5 mg, 9.54 umol, 5.00% yield), 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (20 mg, 38.16 umol, 20.00% yield) and 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (15 mg) as a white solid.MS (ESI) *m/z* 524.2 $[M+H]^+$

Isomer 1:

[0001697] ^1H NMR (400MHz, DMSO-d_6) δ = 11.69 - 11.44 (m, 1H), 8.95 (br d, *J*=7.9 Hz, 1H), 7.87 - 7.75 (m, 1H), 7.68 - 7.43 (m, 1H), 7.33 - 7.20 (m, 1H), 7.14 (s, 1H), 7.11 - 6.97 (m, 1H), 4.99 - 4.75 (m, 1H), 4.50 (t, *J*=8.6 Hz, 1H), 3.83 (br d, *J*=10.4 Hz, 1H), 3.66 (d, *J*=10.6 Hz, 1H), 2.75 - 2.63 (m, 1H), 2.36 - 2.12 (m, 2H), 1.99 (dd, *J*=8.5, 12.2 Hz, 1H), 1.83 - 1.69 (m, 1H), 1.60 (br dd, *J*=9.9, 11.9 Hz, 1H), 1.55 - 1.28 (m, 11H), 1.17 - 1.06 (m, 3H), 1.05 - 0.91 (m, 3H)

[0001698] ^1H NMR (400MHz, DMSO-d_6) δ = 11.07 (br s, 1H), 8.73 (br d, *J*=7.5 Hz, 1H), 7.75 - 7.47 (m, 2H), 7.28 (d, *J*=7.5 Hz, 1H), 7.07 (br t, *J*=7.7 Hz, 2H), 4.91 (br d, *J*=7.3 Hz, 1H), 4.59 (br s, 1H), 3.84 (d, *J*=10.1 Hz, 1H), 3.63 (br s, 1H), 2.30 - 1.92 (m, 3H), 1.78 (br s, 1H), 1.72 - 1.63 (m, 1H), 1.60 - 1.33 (m, 12H), 1.18 (s, 3H), 1.09 (s, 3H)

Isomer 2:

[0001699] ^1H NMR (400MHz, DMSO-d_6) δ = 11.56 (br s, 1H), 9.00 - 8.79 (m, 1H), 7.82 (s, 1H), 7.68 - 7.48 (m, 1H), 7.32 - 7.22 (m, 1H), 7.15 (s, 1H), 7.12 - 6.99 (m, 1H), 4.98 -

4.71 (m, 1H), 4.50 (t, *J*=8.7 Hz, 1H), 3.90 - 3.77 (m, 1H), 3.73 - 3.60 (m, 1H), 2.47 - 2.39 (m, 1H), 2.24 (br dd, *J*=7.9, 12.3 Hz, 1H), 2.17 - 2.08 (m, 1H), 1.98 (br dd, *J*=8.4, 11.9 Hz, 1H), 1.83 - 1.68 (m, 1H), 1.61 - 1.51 (m, 2H), 1.50 - 1.36 (m, 7H), 1.35 - 1.21 (m, 3H), 1.15 (s, 3H), 1.08 - 0.97 (m, 3H)

[0001700] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.09 (br s, 1H), 8.66 (br s, 1H), 7.65 - 7.53 (m, 2H), 7.26 (d, *J*=7.7 Hz, 1H), 7.12 - 6.97 (m, 2H), 4.89 (br d, *J*=5.7 Hz, 1H), 4.57 (br s, 1H), 3.88 - 3.56 (m, 2H), 2.28 - 1.96 (m, 3H), 1.85 - 1.60 (m, 2H), 1.58 - 1.22 (m, 12H), 1.16 (s, 3H), 1.07 (s, 2H), 1.09 - 0.99 (m, 1H)

Isomer 3:

[0001701] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.66 - 11.45 (m, 1H), 8.94 (d, *J*=8.2 Hz, 1H), 7.92 - 7.75 (m, 1H), 7.64 (d, *J*=7.9 Hz, 1H), 7.29 (d, *J*=7.3 Hz, 1H), 7.17 - 7.12 (m, 1H), 7.11 - 6.98 (m, 1H), 5.00 - 4.73 (m, 1H), 4.50 (br t, *J*=8.6 Hz, 1H), 3.83 (br d, *J*=10.4 Hz, 1H), 3.72 - 3.62 (m, 1H), 2.75 - 2.63 (m, 1H), 2.31 - 2.12 (m, 2H), 2.08 - 1.94 (m, 1H), 1.80 - 1.57 (m, 2H), 1.54 - 1.36 (m, 8H), 1.35 - 1.18 (m, 3H), 1.17 - 1.07 (m, 3H), 1.07 - 0.92 (m, 3H)

[0001702] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.07 (br s, 1H), 8.86 - 8.69 (m, 1H), 7.70 - 7.55 (m, 2H), 7.28 (d, *J*=7.5 Hz, 1H), 7.07 (br t, *J*=7.6 Hz, 2H), 4.98 - 4.85 (m, 1H), 4.60 (br s, 1H), 3.84 (d, *J*=10.6 Hz, 1H), 3.64 (s, 1H), 2.29 - 1.96 (m, 3H), 1.77 (br s, 1H), 1.73 - 1.63 (m, 1H), 1.61 - 1.32 (m, 12H), 1.20 - 1.14 (m, 3H), 1.13 - 1.06 (m, 3H)

Isomer 4:

[0001703] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.69 - 11.53 (m, 1H), 9.11 - 8.97 (m, 1H), 7.98 - 7.85 (m, 1H), 7.68 - 7.45 (m, 1H), 7.33 - 7.20 (m, 1H), 7.15 (s, 1H), 7.12 - 6.96 (m, 1H), 4.97 - 4.72 (m, 1H), 4.70 - 4.48 (m, 1H), 3.83 (br d, *J*=10.4 Hz, 1H), 3.72 - 3.59 (m, 1H), 2.70 - 2.54 (m, 1H), 2.35 - 2.12 (m, 3H), 2.01 - 1.53 (m, 3H), 1.53 - 1.39 (m, 6H), 1.39 - 1.27 (m, 4H), 1.20 - 1.01 (m, 6H)

[0001704] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.13 (br s, 1H), 8.85 (br s, 1H), 7.74 - 7.57 (m, 2H), 7.28 (br d, *J*=7.7 Hz, 1H), 7.18 - 6.96 (m, 2H), 4.90 (br s, 1H), 4.62 (br s, 1H), 3.85 (br d, *J*=10.4 Hz, 1H), 3.64 (s, 1H), 2.31 - 2.22 (m, 1H), 2.14 (br s, 2H), 1.89 - 1.75 (m, 1H), 1.73 - 1.64 (m, 1H), 1.60 - 1.28 (m, 12H), 1.20 (s, 3H), 1.14 (s, 3H)

Isomer 5:

[0001705] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.55 (br s, 1H), 9.02 - 8.77 (m, 1H), 7.82 (s, 1H), 7.69 - 7.47 (m, 1H), 7.32 - 7.22 (m, 1H), 7.15 (s, 1H), 7.11 - 6.98 (m, 1H), 4.98 - 4.71 (m, 1H), 4.50 (t, *J*=8.5 Hz, 1H), 3.87 - 3.77 (m, 1H), 3.74 - 3.59 (m, 1H), 2.47 - 2.40 (m, 1H), 2.35 - 2.20 (m, 1H), 2.19 - 2.08 (m, 1H), 1.98 (dd, *J*=8.5, 12.5 Hz, 1H), 1.89 - 1.70 (m, 1H), 1.69 - 1.52 (m, 2H), 1.51 - 1.39 (m, 6H), 1.38 - 1.28 (m, 4H), 1.15 (s, 3H), 1.07 - 0.97 (m, 3H)

[0001706] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.12 (br s, 1H), 8.65 (br s, 1H), 7.67 - 7.52 (m, 2H), 7.28 (d, *J*=7.7 Hz, 1H), 7.14 - 6.92 (m, 2H), 4.91 (br d, *J*=7.1 Hz, 1H), 4.59 (br s, 1H), 3.83 (br d, *J*=11.0 Hz, 1H), 3.63 (s, 1H), 2.31 - 2.20 (m, 1H), 2.19 - 1.96 (m, 2H), 1.81 (br s, 1H), 1.68 (br d, *J*=10.6 Hz, 1H), 1.61 - 1.34 (m, 12H), 1.18 (s, 3H), 1.09 (s, 3H)

Isomer 6:

[0001707] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.69 - 11.50 (m, 1H), 9.10 - 8.98 (m, 1H), 7.97 - 7.88 (m, 1H), 7.68 - 7.45 (m, 1H), 7.33 - 7.19 (m, 1H), 7.15 (s, 1H), 7.11 - 6.97 (m, 1H), 4.96 - 4.71 (m, 1H), 4.69 - 4.47 (m, 1H), 3.83 (br d, *J*=10.1 Hz, 1H), 3.66 (d, *J*=10.4 Hz, 1H), 2.69 - 2.54 (m, 1H), 2.39 - 2.12 (m, 3H), 1.97 - 1.56 (m, 2H), 1.55 - 1.47 (m, 3H), 1.42 (br s, 4H), 1.38 - 1.28 (m, 4H), 1.21 - 1.01 (m, 6H)

[0001708] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.12 (br s, 1H), 8.84 (br d, *J*=7.3 Hz, 1H), 7.74 - 7.56 (m, 2H), 7.28 (br d, *J*=7.5 Hz, 1H), 7.07 (br t, *J*=7.6 Hz, 2H), 4.89 (br s, 1H), 4.61 (br s, 1H), 3.84 (br d, *J*=10.4 Hz, 1H), 3.62 (br s, 1H), 2.29 - 2.06 (m, 3H), 1.85 - 1.61 (m, 2H), 1.59 - 1.33 (m, 12H), 1.20 (s, 3H), 1.14 (s, 3H)

Step 8: 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[0001709] The white solid was separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 55%-55%,10min) to give

[0001710] 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (18 mg, 34.35 umol, 60.00%

yield) and 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (4 mg, 7.63 umol, 13.33% yield) as a white solid. MS (ESI) *m/z* 524.2 $[M+H]^+$

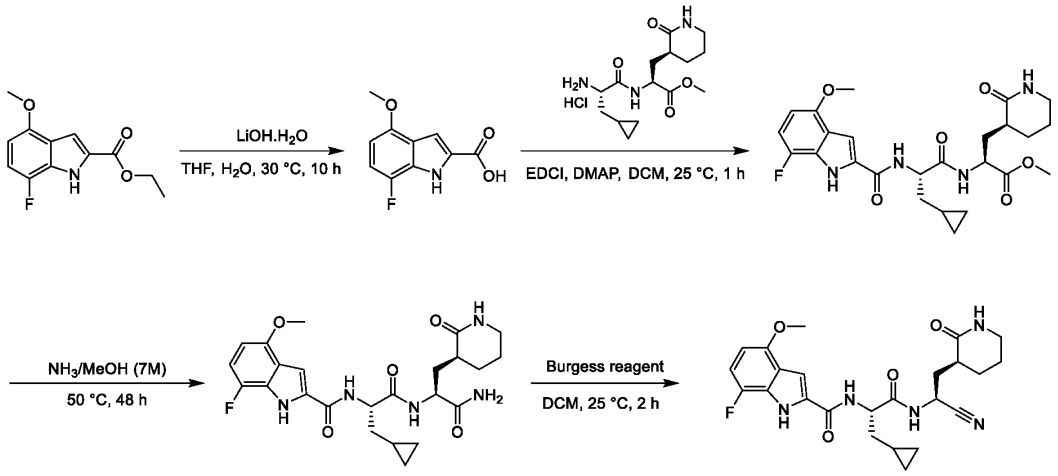
[0001711] Isomer 1:

[0001712] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.68 - 11.45 (m, 1H), 8.95 (br d, *J*=7.9 Hz, 1H), 7.86 - 7.76 (m, 1H), 7.68 - 7.44 (m, 1H), 7.33 - 7.20 (m, 1H), 7.14 (s, 1H), 7.11 - 6.97 (m, 1H), 4.98 - 4.77 (m, 1H), 4.50 (br t, *J*=8.5 Hz, 1H), 3.83 (br d, *J*=10.1 Hz, 1H), 3.66 (br d, *J*=10.1 Hz, 1H), 2.76 - 2.63 (m, 1H), 2.36 - 2.10 (m, 2H), 2.05 - 1.94 (m, 1H), 1.82 - 1.56 (m, 2H), 1.54 - 1.18 (m, 11H), 1.17 - 1.06 (m, 3H), 1.05 - 0.92 (m, 3H).

[0001713] Isomer 2:

[0001714] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.58 (br s, 1H), 9.10 - 8.90 (m, 1H), 7.89 (s, 1H), 7.70 - 7.44 (m, 1H), 7.30 (d, *J*=7.5 Hz, 1H), 7.16 (s, 1H), 7.12 - 6.99 (m, 1H), 4.94 - 4.82 (m, 1H), 4.51 (t, *J*=8.6 Hz, 1H), 3.81 (br d, *J*=10.4 Hz, 1H), 3.70 (br d, *J*=10.4 Hz, 1H), 2.30 - 2.10 (m, 2H), 2.03 (dd, *J*=8.5, 12.0 Hz, 1H), 1.81 - 1.65 (m, 1H), 1.62 - 1.18 (m, 13H), 1.16 - 1.01 (m, 6H).

Example 212. Synthesis of viral protease inhibitor compound 820



Step 1: 7-fluoro-4-methoxy-1H-indole-2-carboxylic acid

[0001715] To a solution of ethyl 7-fluoro-4-methoxy-1H-indole-2-carboxylate (800 mg, 3.37 mmol, 1 *eq*) in THF (10 mL) and H_2O (5 mL) was added $LiOH·H_2O$ (283.03 mg,

6.74 mmol, 2 *eq*), and then the mixture was stirred at 30 °C for 10 h. Upon completion, the pH of the reaction mixture was adjust to about 3 with HCl aq (1M). The mixture was extracted with EtOAc (100 mL * 3). The combined organic layer was dried over Na_2SO_4, filtered, concentrated to give product 7-fluoro-4-methoxy-1H-indole-2-carboxylic acid (680 mg, crude) as white solid. MS (ESI) *m/z* 210.0 $[M+H]^+$

Step 2: (S)-methyl 2-((S)-3-cyclopropyl-2-(7-fluoro-4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001716] To a solution of 7-fluoro-4-methoxy-1H-indole-2-carboxylic acid (0.68 g, 3.25 mmol, 1 *eq*) in DCM (20 mL) was added (*S*)-methyl 2-((*S*)-2-amino-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1.24 g, 3.58 mmol, 1.1 *eq*, HCl), EDCI (1.25 g, 6.50 mmol, 2 *eq*), DMAP (1.19 g, 9.75 mmol, 3 *eq*) and the mixture was stirred at 25 °C for 1 h. Upon completion, the reaction was quenched by the addition of H_2O (200 mL) and then extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by column chromatography (SiO_2, EtOAc:MEOH = 10:1) to give product (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(7-fluoro-4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1.15 g, 2.11 mmol, 65.01% yield, 92.35% purity) as white solid. MS (ESI) *m/z* 503.2 $[M+H]^+$

Step 3: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide

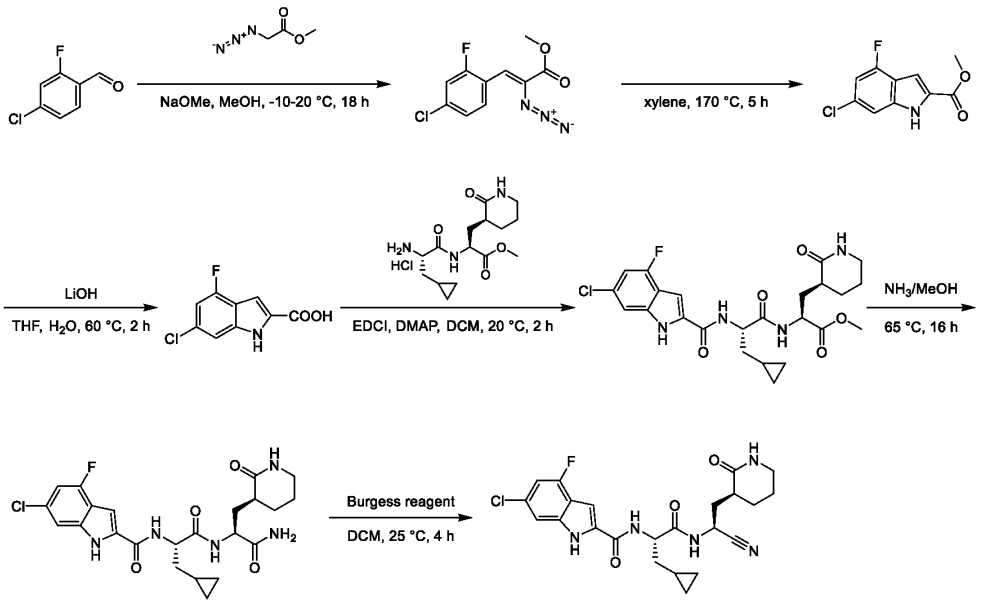
[0001717] To a solution of (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(7-fluoro-4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1.08 g, 2.15 mmol, 1 *eq*) in NH_3 (7 M in MeOH, 60 mL, 195.43 *eq*) was stirred at 50 °C for 48 h. Upon completion, the reaction was concentrated in the vacuum to give crude product N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide (1.06 g, crude) as white solid. MS (ESI) *m/z* 488.2 $[M+H]^+$

Step 4: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide

[0001718] To a solution of N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide (1.03 g, 2.11 mmol, 1 *eq*) in DCM (60 mL) was added Burgess reagent (1.51 g, 6.34 mmol, 3 *eq*), and the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was concentrated in the vacuum and was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 20%-50%,8min) to give N-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide (400 mg, 845.40 umol, 40.01% yield, 99.23% purity) as white solid. MS (ESI) *m/z* 470.1 $[M+H]^+$

[0001719] ^1H NMR (400MHz, DMSO-d_6) δ = 8.95 - 8.94 (m, 1H), 8.57 - 8.55 (m, 1H), 7.54 (br s, 1H), 7.36 - 7.33 (m, 1H), 6.95 - 6.90 (m, 1H), 6.43 - 6.40 (m, 1H), 5.09 - 5.04 (m, 1H), 4.52 - 4.41 (m, 1H), 3.87 (s, 3H), 3.15 - 3.03 (m, 2H), 2.33 - 2.19 (m, 2H), 1.89 - 1.75 (m, 3H), 1.72 - 1.69 (m, 1H), 1.64 - 1.52 (m, 1H), 1.51 - 1.34 (m, 2H), 0.86 - 0.76 (m, 1H), 0.47 - 0.37 (m, 2H), 0.24 - 0.15 (m, 1H), 0.14 - 0.06 (m, 1H).

Example 213. Synthesis of viral protease inhibitor compound 838



Step 1: methyl (Z)-2-azido-3-(4-chloro-2-fluoro-phenyl)prop-2-enoate

[0001720] A mixture of NaOMe (3.41 g, 63.07 mmol, 2 eq) in MeOH (40 mL) was cooled to -10 °C, and then a mixture 4-chloro-2-fluoro-benzaldehyde (5 g, 31.53 mmol, 1 eq) and methyl 2-azidoacetate (7.26 g, 63.07 mmol, 2 eq) with MeOH (10 mL) was added dropwise. The mixture was stirred at 20 °C for 18 h. Upon completion, the reaction mixture was quenched by the addition ot H_2O (20 mL) at 25 °C, diluted with H_2O 100 mL and extracted with ethyl acetate (100 mL * 2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0) to afford methyl (Z)-2-azido-3-(4-chloro-2-fluoro-phenyl)prop-2-enoate (4 g, 14.87 mmol, 47.14% yield, 95% purity) as a white solid.

Step 2: methyl 6-chloro-4-fluoro-1H-indole-2-carboxylate

[0001721] A mixture of methyl (Z)-2-azido-3-(4-chloro-2-fluoro-phenyl)prop-2-enoate (4 g, 15.65 mmol, 1 eq) in xylene (20 mL) was stirred at 170 °C for 5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The crude product was triturated with petroleum ether: ethyl acetate = 10:1 to afford methyl 6-chloro-4-fluoro-1H-indole-2-carboxylate (2 g, 8.35 mmol, 53.35% yield, 95% purity) as a white solid.

Step 3: 6-chloro-4-fluoro-1H-indole-2-carboxylic acid

[0001722] To a mixture of methyl 6-chloro-4-fluoro-1H-indole-2-carboxylate (1.4 g, 6.15 mmol, 1 eq) in THF (10 mL) and H_2O (5 mL) was added $LiOH·H_2O$ (516.20 mg, 12.30 mmol, 2 eq). After stirring at 60 °C for 2 h, the pH of the reaction mixture was adjusted to 3 with HCl (1 M), and then diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine 30 mL (30 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was used next step directly. Compound 6-chloro-4-fluoro-1H-indole-2-carboxylic acid (1.3 g, 5.78 mmol, 94.01% yield, 95% purity) was obtained as a white solid.

Step 4: methyl (2S)-2-[[(2S)-2-[(6-chloro-4-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001723] To a mixture of 6-chloro-4-fluoro-1H-indole-2-carboxylic acid (600 mg, 2.81 mmol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-

2-oxo-3-piperidyl]propanoate (977.10 mg, 2.81 mmol, 1 *eq*, HCl) in DCM (2 mL) and DMF (1 mL) was added EDCI (1.08 g, 5.62 mmol, 2 *eq*) and DMAP (686.36 mg, 5.62 mmol, 2 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL * 2). The combined organic layers were washed with brine (100 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 8/1 to 0/1) to get the compound methyl (2S)-2-[[(2S)-2-[(6-chloro-4-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl] amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.1 g, 1.95 mmol, 69.52% yield, 90% purity) as a white solid. MS (ESI) *m/z* 507.2 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-4-fluoro-1H-indole-2-carboxamide

[0001724] A solution of methyl (2S)-2-[[(2S)-2-[(6-chloro-4-fluoro-1H-indole-2-carbonyl)amino]-3- cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 1.97 mmol, 1 eq) in NH_3/MeOH (7 M, 20 mL, 70.97 eq) was stirred at 65 °C for 16 h. Upon completion, the reaction mixture concentrated under reduced pressure to give a residue and used next step directly. Compound N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl] amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-4-fluoro-1H-indole-2-carboxamide (950 mg, 1.74 mmol, 88.11% yield, 90% purity) was obtained as a white solid. MS (ESI) *m/z* 492.2 $[M+H]^+$

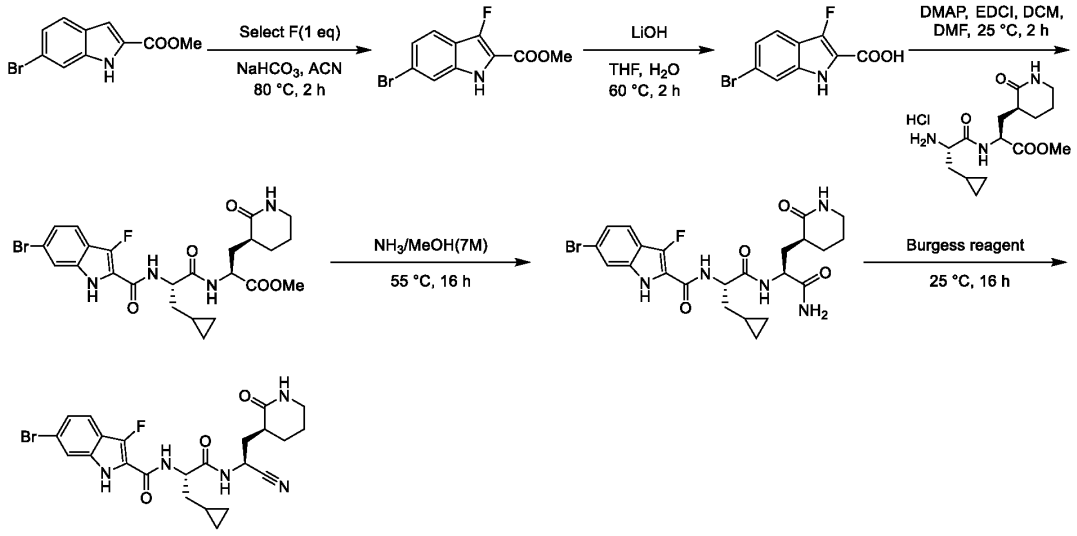
Step 6: 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-fluoro-1H-indole-2-carboxamide

[0001725] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1- (cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-4-fluoro-1H-indole-2-carboxamide (500 mg, 1.02 mmol, 1 eq) in DCM (20 mL) was added Burgess reagent (484.42 mg, 2.03 mmol, 2 eq). The mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was diluted with H_2O (5 mL) and extracted with DCM (20 mL * 2). The combined organic layers were concentrated with using blow-dry to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 40%-

70%,10min) to get 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-fluoro-1H-indole-2-carboxamide (120 mg, 253.20 umol, 24.91% yield, 100% purity) as a white solid. MS (ESI) *m/z* 474.1 $[M+H]^+$

[0001726] ^1H NMR (400MHz, DMSO-d_6) δ = 12.08 (br s, 1H), 8.94 (d, *J*=8.0 Hz, 1H), 8.73 (d, *J*=7.5 Hz, 1H), 7.61 - 7.23 (m, 3H), 6.99 (d, *J*=10.1 Hz, 1H), 5.06 (q, *J*=8.1 Hz, 1H), 4.57 - 4.37 (m, 1H), 3.18 - 2.98 (m, 2H), 2.37 - 2.17 (m, 2H), 1.89 - 1.26 (m, 7H), 0.89 - 0.65 (m, 1H), 0.51 - 0.32 (m, 2H), 0.27 - 0.01 (m, 2H).

Example 214. Synthesis of viral protease inhibitor compound 848



Step 1: methyl 6-bromo-3-fluoro-1H-indole-2-carboxylate

[0001727] To a mixture of methyl 6-bromo-1H-indole-2-carboxylate (2 g, 7.87 mmol, 1 *eq*) in ACN (84 mL) was added $NaHCO_3$ (36.42 g, 433.52 mmol, 16.86 mL, 55.07 *eq*) in one portion at 25 °C. Select F (3.07 g, 8.66 mmol, 1 eq) was added and stirred at 80 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give a crude product. The crude was purified by prep-HPLC (neutral condition, column: Agela DuraShell C18 250*50mm*10um;mobile phase: [water(10 mM NH4HCO3)-ACN];B%: 50%-55%, 20 min) to give methyl 6-bromo-3-fluoro-1H-indole-2-carboxylate (500 mg, 1.84 mmol, 23.35% yield) as a yellow solid.

Step 2: 6-bromo-3-fluoro-1H-indole-2-carboxylic acid

[0001728] To a mixture of methyl 6-bromo-3-fluoro-1H-indole-2-carboxylate (500 mg, 1.84 mmol, 1 *eq*) in THF (5 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (154.22 mg, 3.68 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 60 °C for 2 h. Upon completion, the reaction mixture was adjusted to acidity by 1M HCl and extracted with ethyl acetate (6 mL * 3). The combined organic layers were washed with brine (9 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-bromo-3-fluoro-1H-indole-2-carboxylic acid (440 mg, 1.71 mmol, 92.78% yield) as a yellow solid. (ESI) *m/z* 256.0 $[M-H]^+$

Step 3: methyl (2S)-2-[[(2S)-2-[(6-bromo-3-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001729] To a mixture of 6-bromo-3-fluoro-1H-indole-2-carboxylic acid (440 mg, 1.71 mmol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (654.28 mg, 1.88 mmol, 1.1 *eq*, HCl) in DCM (8 mL) and DMF (2 mL) was added DMAP (626.73 mg, 5.13 mmol, 3 *eq*) and EDCI (655.61 mg, 3.42 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H2O (20 mL) and extracted with ethyl acetate (15 mL * 4). The combined organic layers were washed with brine 30 mL (30 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=5/1 to 0/1) to give methyl (2S)-2-[[(2S)-2-[(6-bromo-3-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (510 mg, 924.91 umol, 54.09% yield) as a white solid. (ESI) *m/z* 551.1 $[M+H]^+$

Step 4: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-bromo-3-fluoro-1H-indole-2-carboxamide

[0001730] A mixture of methyl (2S)-2-[[(2S)-2-[(6-bromo-3-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (510 mg, 924.91 umol, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 75.68 *eq*) was stirred at 55 °C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-

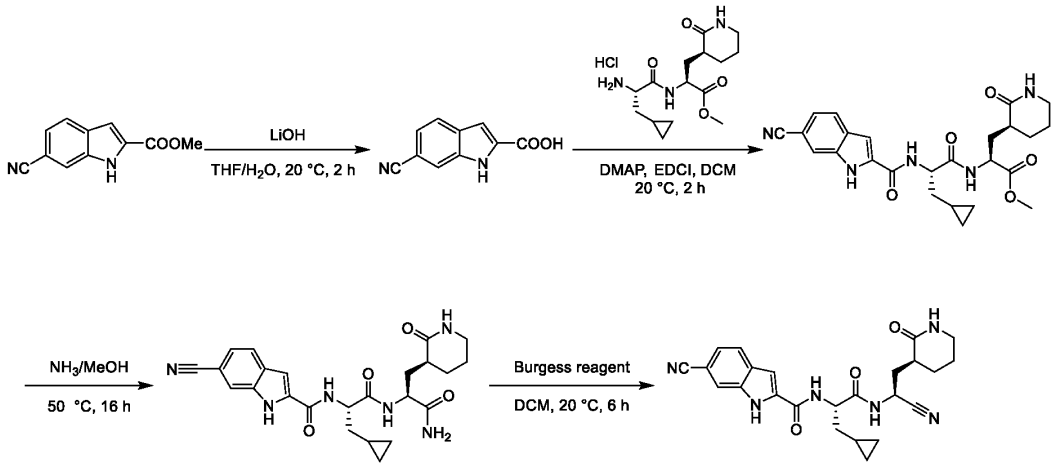
piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-bromo-3-fluoro-1H-indole-2-carboxamide (500 mg, crude) as a yellow solid. MS (ESI) *m/z* 536.2 $[M+H]^+$

Step 5: 6-bromo-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-3-fluoro-1H-indole-2-carboxamide

[0001731] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-bromo-3-fluoro-1H-indole-2-carboxamide (500 mg, 745.72 umol, 80% purity, 1 *eq*) in DCM (8 mL) was added Burgess reagent (533.14 mg, 2.24 mmol, 3 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition; column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 40%-65%,8min) to give 6-bromo-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-3-fluoro-1H-indole-2-carboxamide (170 mg, 327.95 umol, 43.98% yield) as a white solid. MS (ESI) *m/z* 518.1 $[M+H]^+$

[0001732] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.70 (s, 1H), 8.98 (d, *J*=7.9 Hz, 1H), 7.84 (dd, *J*=3.1, 7.3 Hz, 1H), 7.65 - 7.58 (m, 2H), 7.55 (br s, 1H), 7.26 (dd, *J*=1.5, 8.6 Hz, 1H), 5.09 (q, *J*=8.1 Hz, 1H), 4.57 - 4.49 (m, 1H), 3.13 - 3.05 (m, 2H), 2.30 - 2.20 (m, 2H), 1.82 (dt, *J*=6.6, 14.0 Hz, 3H), 1.77 - 1.67 (m, 1H), 1.64 - 1.51 (m, 2H), 1.47 - 1.35 (m, 1H), 0.81 - 0.70 (m, 1H), 0.48 - 0.37 (m, 2H), 0.21 - 0.07 (m, 2H)

Example 215. Synthesis of viral protease inhibitor compound 862



Step 1: 6-cyano-1H-indole-2-carboxylic acid

[0001733] To a solution of methyl 6-cyano-1H-indole-2-carboxylate (1 g, 5.00 mmol, 1 eq) in H_2O (4 mL) and THF (8 mL) was added $LiOH.H_2O$ (358.88 mg, 14.99 mmol, 3 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give 6-cyano-1H-indole-2-carboxylic acid (805 mg, crude) as a white solid. MS (ESI) *m/z* 187.0 $[M+H]^+$

Step 2: methyl (2S)-2-[[(2S)-2-[(6-cyano-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001734] To a solution of 6-cyano-1H-indole-2-carboxylic acid (776.06 mg, 4.17 mmol, 1 eq) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.45 g, 4.17 mmol, 1 eq, HCl) in DCM (50 mL) was added DMAP (1.53 g, 12.51 mmol, 3 eq) and EDCI (2.40 g, 12.51 mmol, 3 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL), and then extracted with DCM (10 mL * 2). The combined organic layers were washed with HCl (1M) 20 mL (10 mL * 2), then were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1 to 0/1, dichloromethane : methanol = 10:1, (UV 254 nm)) to give methyl (2S)-2-[[(2S)-2-[(6-cyano-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.3 g, 2.56 mmol, 61.46% yield, 94.5% purity) as a white solid. MS (ESI) *m/z* 480.2 $[M+H]^+$

Step 3: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-cyano-1H-indole-2-carboxamide

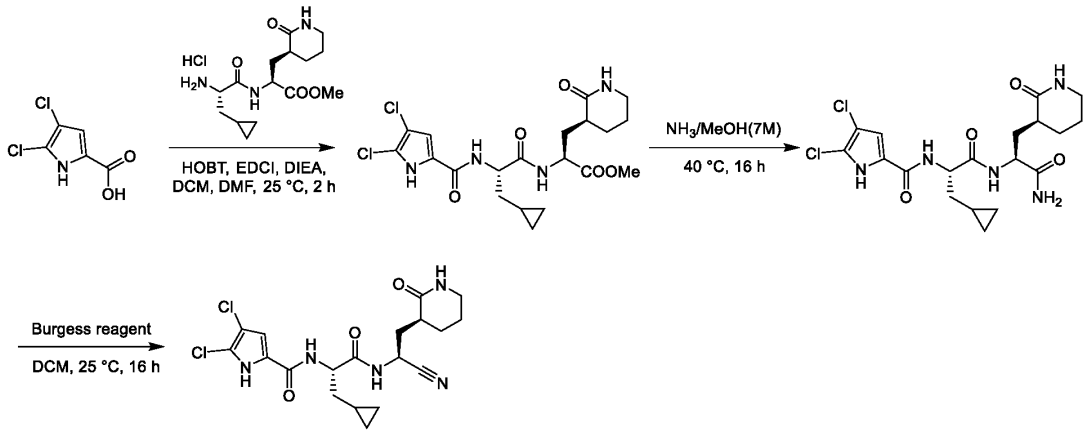
[0001735] A solution of methyl (2S)-2-[[(2S)-2-[(6-cyano-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.2 g, 2.50 mmol, 1 eq) in NH_3/MeOH (7 M, 20 mL, 55.94 eq) was stirred at 50 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove solvent to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-cyano-1H-indole-2-carboxamide (1.1 g, crude) as a white solid. MS (ESI) *m/z* 465.2 $[M+H]^+$

Step 4: 6-cyano-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001736] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-cyano-1H-indole-2-carboxamide (1 g, 2.15 mmol, 1 eq) in DCM (20 mL) was added Burgess reagent (1.03 g, 4.31 mmol, 2 eq). The mixture was stirred at 20 °C for 6 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150*50mm* 10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-55%,10min) to give 6-cyano-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (414.8 mg, 929.00 umol, 43.15% yield, 100% purity) as a white solid. MS (ESI) *m/z* 447.2 $[M+H]^+$.

[0001737] 1H NMR (400MHz, DMSO-d_6) δ = 12.08 (s, 1H), 8.96 (d, *J* = 8.4Hz, 1H), 8.82 (d, *J* = 7.8Hz, 1H), 7.89 - 7.81 (m, 2H), 7.53 (s, 1H), 7.45 - 7.33 (m, 2H), 5.07 (q, *J* = 8.2Hz, 1H), 4.54 - 4.46 (m, 1H), 3.17 - 3.01 (m, 2H), 2.35 - 2.20 (m, 2H), 1.91 - 1.65 (m, 4H), 1.63 - 1.32 (m, 3H), 0.88 - 0.73 (m, 1H), 0.50 - 0.35 (m, 2H), 0.25 - 0.07 (m, 2H)

Example 216. Synthesis of viral protease inhibitor compound 866



Step 1: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,5-dichloro-1H-pyrrole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001738] To a mixture of 4,5-dichloro-1H-pyrrole-2-carboxylic acid (300 mg, 1.67 mmol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (637.74 mg, 1.83 mmol, 1.1 *eq*, HCl) in DCM (8 mL) and DMF (2 mL) was added DIEA (430.84 mg, 3.33 mmol, 580.64 uL, 2 *eq*), HOBt (450.44 mg, 3.33 mmol, 2 eq) and EDCI (639.05 mg, 3.33 mmol, 2 eq) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (15 mL * 4). The combined organic layers were washed with brine (30 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=5/1 to 0/1) to give methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,5-dichloro-1H-pyrrole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (550 mg, 1.16 mmol, 69.71% yield) as a white solid. MS (ESI) m/z 473.1 $[M+H]^+$

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5-dichloro-1H-pyrrole-2-carboxamide

[0001739] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,5-dichloro-1H-pyrrole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (500 mg, 1.06 mmol, 1 *eq*) in NH_3/MeOH (7 M, 20 mL, 132.54 *eq*) was stirred at 40 °C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-

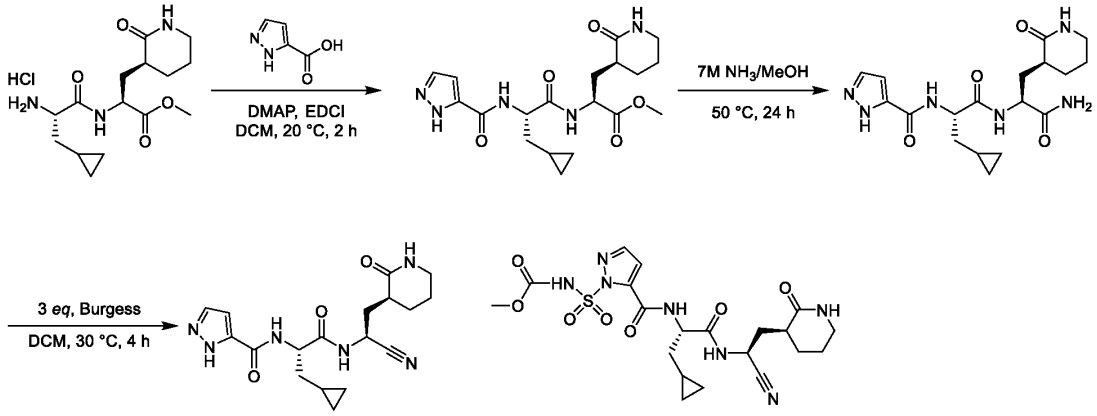
(cyclopropylmethyl)-2-oxo-ethyl]-4,5-dichloro-1H-pyrrole-2-carboxamide (480 mg, 1.05 mmol, 99.14% yield) as a yellow solid. MS (ESI) m/z 458.1 $[M+H]^+$

Step 3: 4,5-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-pyrrole-2-carboxamide

[0001740] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,5-dichloro-1H-pyrrole-2-carboxamide (480 mg, 555.05 umol, 53% purity, 1 *eq*) in DCM (8 mL) was added Burgess reagent (396.82 mg, 1.67 mmol, 3 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition; column: column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 25%-50%,8min) to give 4,5-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-pyrrole-2-carboxamide (108 mg, 245.27 umol, 44.19% yield) as a white solid. MS (ESI) m/z 440.1 $[M+H]^+$

[0001741] ^1H NMR (400MHz, DMSO-d_6) δ = 12.74 (br s, 1H), 8.88 (d, J=8.2 Hz, 1H), 8.22 (br d, J=7.1 Hz, 1H), 7.53 (br s, 1H), 7.05 (s, 1H), 5.10 - 5.00 (m, 1H), 4.44 - 4.33 (m, 1H), 3.15 - 3.02 (m, 2H), 2.30 - 2.17 (m, 2H), 1.91 - 1.65 (m, 4H), 1.55 (br dd, J=3.5, 9.9 Hz, 1H), 1.47 - 1.32 (m, 2H), 0.82 - 0.70 (m, 1H), 0.45 - 0.34 (m, 2H), 0.21 - 0.02 (m, 2H)

Example 217. Synthesis of viral protease inhibitor compound 872



Step 1: (S)-methyl2-((S)-3-cyclopropyl-2-(1H-pyrazole-5-carboxamido)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001742] To a solution of 1*H*-pyrazole-5-carboxylic acid (500 mg, 4.46 mmol, 1 *eq*) and methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (1.24 g, 3.57 mmol, 0.8 *eq*, HCl) in DCM (40 mL) was added DMAP (1.09 g, 8.92 mmol, 2 *eq*) and EDCI (1.71 g, 8.92 mmol, 2 *eq*), and then the mixture was stirred at 20 °C for 2 h. Upon the reaction completement, the mixture was poured into water (40 mL) and was extracted with DCM (15 mL * 3) and dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and was purified by prep-HPLC (column: Waters Xbridge C18 150 * 50mm * 10um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 1%-40%, 10 min) to obtained (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(1*H*-pyrazole-5-carboxamido)propanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (550 mg, 1.26 mmol, 28.25% yield, 92.9% purity) as a white solid. MS (ESI) *m/z* 406.2 $[M+H]^+$

Step 2: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrazole-5-carboxamide

[0001743] A solution of (*S*)-methyl 2-((*S*)-3-cyclopropyl-2- (1*H*-pyrazole-5-carboxamido) propanamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (500 mg, 1.23 mmol, 1 *eq*) in NH_3/MeOH (20 mL, 7M) was stirred at 50 °C for 24 h. Upon the reaction completement, the mixture was concentrated in vacuum to obtain *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1*H*-pyrazole-5-carboxamide (500 mg, crude) as a light yellow solid. MS (ESI) *m/z* 391.2 $[M+H]^+$

Step 3: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrazole-5-carboxamide & methyl(5-(((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamoyl)-1H-pyrazol-1-yl)sulfonylcarbamate

[0001744] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1*H*-pyrazole-5-carboxamide (500 mg, 1.28 mmol, 1 *eq*) in DCM (8 mL) was added Burgess reagent (915.53 mg, 3.84 mmol, 3 *eq*), and then the mixture was stirred at 30 °C for 4 h. Upon completion of the reaction, the reaction mixture was quenched with water (1 mL) and was dried with using

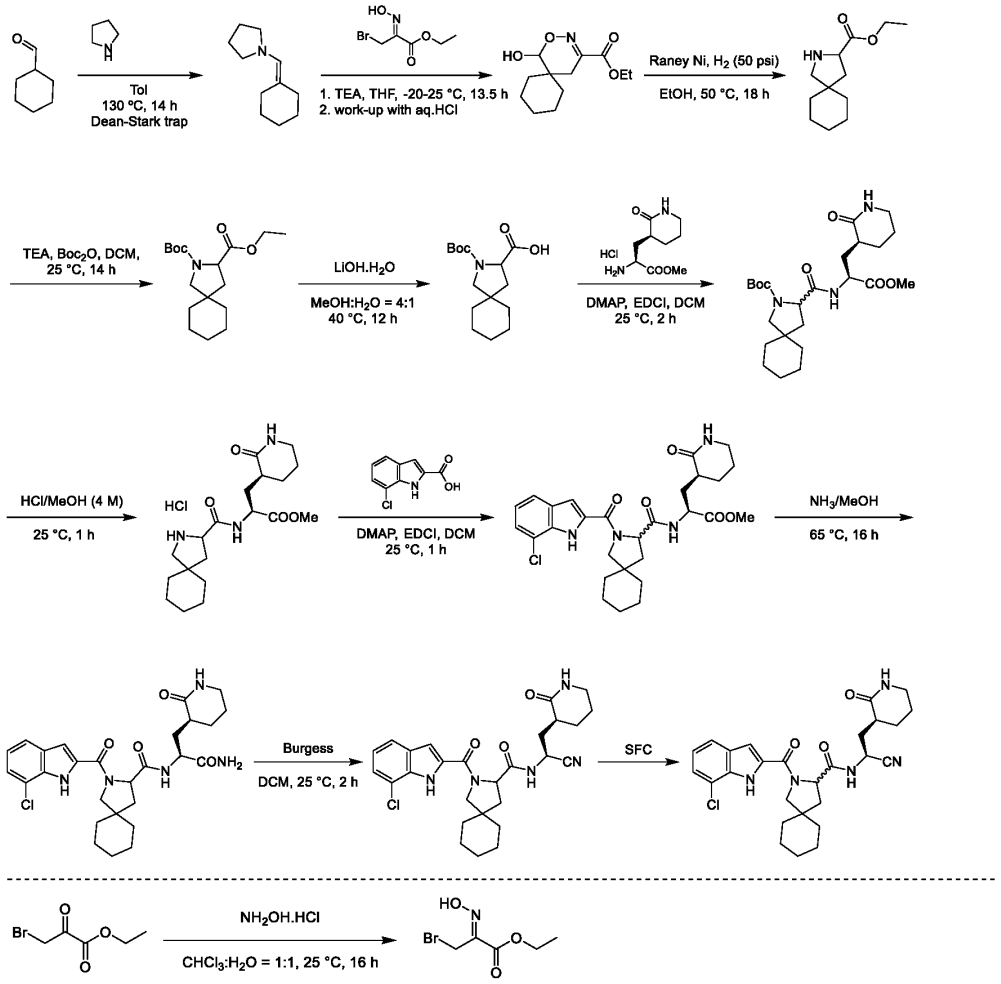
N_2, and then was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40mm * 10um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 15%-45%, 8min) to obtain *N*-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-xopropan2-yl)-1*H*-pyrazole-5-carboxamide (compound 872, 160 mg, 425.76 umol, 33.25% yield, 99.1% purity) as a white solid. MS (ESI) *m/z* 373.1[M+H]$^+$

[0001745] ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 13.57 - 13.18 (m, 1H), 8.91 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.52 (s, 1H), 7.02 - 6.59 (m, 1H), 5.05 (q, *J* = 7.9 Hz, 1H), 4.48 (q, *J* = 7.4 Hz, 1H), 3.16 - 3.02 (m, 2H), 2.31 - 2.17 (m, 2H), 1.89 - 1.65 (m, 4H), 1.63 - 1.32 (m, 3H), 0.71 (d, *J* = 6.4 Hz, 1H), 0.40 (d, *J* = 8.0 Hz, 2H), 0.09 (dd, *J* = 4.6, 14.9 Hz, 2H).

[0001746] Methyl(5-(((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl -1-oxopropan-2-yl)carbamoyl)-1*H*-pyrazol-1-yl)sulfonylcarbamate (20 mg, 425.76 umol, 33.25% yield, 99.1% purity) was obtained as a white solid. MS (ESI) *m/z* 510.1[M+H]$^+$

[0001747] ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 9.06 (s, 1H), 8.91 (d, *J* = 8.0 Hz, 1H), 8.03 (s, 1H), 7.77 (s, 1H), 7.52 (s, 1H), 7.21 (s, 1H), 7.08 (s, 1H), 7.01 - 6.92 (m, 1H), 6.77 - 6.32 (m, 2H), 5.05 (q, *J* = 7.9 Hz, 1H), 4.56 - 4.40 (m, 1H), 3.47 (s, 3H), 3.16 - 3.01 (m, 2H), 2.30 - 2.15 (m, 2H), 1.89 - 1.65 (m, 4H), 1.63 - 1.31 (m, 3H), 0.77 - 0.65 (m, 1H), 0.45 - 0.32 (m, 2H), 0.21 - 0.00 (m, 2H).

Example 218. Synthesis of viral protease inhibitor compound 731



Step 1: (Z)-ethyl 3-bromo-2-(hydroxyimino)propanoate

[0001748] To a solution of ethyl 3-bromo-2-oxo-propanoate (167 g, 428.18 mmol, 107.05 mL, 50% purity, 1 *eq*) in $CHCl_3$ (800 mL) was added $NH_2OH.HCl$ (32.73 g, 471.00 mmol, 1.1 *eq*) in H_2O (800 mL) under N_2. The mixture was stirred at 25 °C for 16 h. Upon completion, the reaction was extracted with DCM (1000 mL * 4). The combined organic phase was washed with brine (2000 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give (Z)-ethyl 3-bromo-2-(hydroxyimino)propanoate (440 g, crude) as a white solid. MS (ESI) *m/z* 210.3 $[M+H]^+$.

Step 2: 1-(cyclohexylidenemethyl)pyrrolidine

[0001749] A mixture of cyclohexanecarbaldehyde (100 g, 891.51 mmol, 107.30 mL, 1 *eq*), pyrrolidine (82.43 g, 1.16 mol, 96.74 mL, 1.3 eq) in toluene (1.6 L) was heated to 130 °C

for 14 h, and then water was removed by Dean-Stark trap. Upon completion, the reaction mixture was concentrated under reduced pressure at 55 °C to afford 1-(cyclohexylidenemethyl)pyrrolidine (420 g, crude) as a yellow oil. MS (ESI) *m/z* 166.2 $[M+H]^+$.

Step 3: ethyl 1-hydroxy-2-oxa-3-azaspiro[5.5]undec-3-ene-4-carboxylate

[0001750] To a solution of 1-(cyclohexylidenemethyl)pyrrolidine (140 g, 847.08 mmol, 1 *eq*) in THF (1000 mL) was added a solution of ethyl (2Z)-3-bromo-2-hydroxyimino-propanoate (177.91 g, 847.08 mmol, 1 *eq*) in THF (1000 mL) drop-wise at -20 °C under N_2. After 1 h, TEA (85.72 g, 847.08 mmol, 117.90 mL, 1 *eq*) was added drop-wise at -20 °C under N_2. The reaction mixture was stirred at 25 °C for 12 h under N_2. Upon completion, the residue was poured into HCl (2M, 2500 mL) and stirred for 30 min, and extracted with ethyl acetate (1500 mL * 4). The combined organic layers were washed with brine (2000 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 1/1) to give a ethyl 1-hydroxy-2-oxa-3-azaspiro[5.5]undec-3-ene-4-carboxylate (200 g, 497.34 mmol, 19.57% yield, 60% purity) as a yellow oil. MS (ESI) *m/z* 242.2 $[M+H]^+$.

Step 4: ethyl 2-azaspiro[4.5]decane-3-carboxylate

[0001751] To a solution of ethyl 1-hydroxy-2-oxa-3-azaspiro[5.5]undec-3-ene-4-carboxylate (20 g, 49.73 mmol, 60% purity, 1 *eq*) in EtOH (150 mL) was added Raney nickel (12.00 g, 140.07 mmol, 2.82 *eq*) under Ar_2. The suspension was degassed under vacuum and purged with H_2 (100.46 mg, 49.73 mmol, 1 *eq*) several times. The mixture was stirred under H_2 (100.46 mg, 49.73 mmol, 1 *eq*) (50 psi) at 50 °C for 18 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 20/1 to ethyl acetate:MeOH = 10/1) to give a ethyl 2-azaspiro[4.5]decane-3-carboxylate (35 g, 165.64 mmol, 33.31% yield) as a yellow oil. MS (ESI) *m/z* 212.2 $[M+H]^+$.

Step 5: 2-tert-butyl 3-ethyl 2-azaspiro[4.5]decane-2,3-dicarboxylate

[0001752] To a solution of ethyl 2-azaspiro[4.5]decane-3-carboxylate (35 g, 132.51 mmol, 80% purity, 1 *eq*) in DCM (350 mL) was added Boc_2O (34.70 g, 159.02 mmol, 36.53 mL,

1.2 *eq*) and TEA (26.82 g, 265.03 mmol, 36.89 mL, 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 14 h. Upon completion, the reaction mixture was quenched by addition H_2O (400 mL), and extracted with ethyl acetate (200 mL * 3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 10/1) to give 2-tert-butyl 3-ethyl 2-azaspiro[4.5]decane-2,3-dicarboxylate (40 g, 95.05 mmol, 71.73% yield, 74% purity) as a yellow oil. MS (ESI) *m/z* 312.2 $[M+H]^+$.

Step 6: 2-(tert-butoxycarbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid

[0001753] To a solution of 2-tert-butyl 3-ethyl 2-azaspiro[4.5]decane-2,3-dicarboxylate (40 g, 128.45 mmol, 1 *eq*) in H_2O (120 mL) and MeOH (480 mL) was added $LiOH.H_2O$ (16.17 g, 385.34 mmol, 3 *eq*). The mixture was stirred at 40 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O (800 mL) and extracted with ethyl acetate (500 mL * 2). The aqueous phase were added with HCl (aq) to adjust the pH to 2 and extracted with ethyl acetate (900 mL * 3). The combined organic layers were washed with brine (900 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (35 g, crude) as a yellow oil. MS (ESI) *m/z* 284.2 $[M+H]^+$

Step 7: tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate

[0001754] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (22.97 g, 97.05 mmol, 1.1 *eq*, HCl) and 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (25 g, 88.23 mmol, 1 *eq*) in DCM (400 mL) was added DMAP (21.56 g, 176.45 mmol, 2 *eq*) and EDCI (25.37 g, 132.34 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was quenched by 0.5 M HCl (400 mL) and then extracted with DCM (150 mL * 3). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/1 to 0/1) to give tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-

piperidyl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (27 g, 47.84 mmol, 54.23% yield, 82.5% purity) as a yellow solid. MS (ESI) *m/z* 466.2 $[M+H]^+$

Step 8: (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate

[0001755] To a solution of *tert*-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (27 g, 47.84 mmol, 82.5% purity, 1 *eq*) in HCl/MeOH (300 mL). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove HCl/MeOH, and added DCM (150 mL) (three times) was concentrated under reduced pressure to give methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (25 g, crude, HCl) as a yellow solid. MS (ESI) *m/z* 366.3 $[M+H]^+$

Step 9: (2S)-methyl 2-(2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001756] To a solution of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (25 g, 62.20 mmol, 1 *eq*, HCl) and 7-chloro-1H-indole-2-carboxylic acid (13.38 g, 68.42 mmol, 1.1 *eq*) in DCM (400 mL) was added EDCI (17.89 g, 93.30 mmol, 1.5 *eq*) and DMAP (15.20 g, 124.40 mmol, 2 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction was quenched by 0.5 M HCl (400 mL) and then extracted with DCM (300 mL * 2). The combined organic phase was washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/1 to 0/1) to give methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (25 g, 44.19 mmol, 71.05% yield, 96% purity) as a yellow solid. MS (ESI) *m/z* 543.3 $[M+H]^+$

Step 10: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001757] A solution of methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (5 g, 8.84 mmol, 96% purity, 1 *eq*) in NH_3 (7 M in MeOH, 57.60 mL, 45.62 *eq*) (15 Psi) was stirred

at 65 °C for 16 h in a 100 mL of autoclave. Upon completion, the reaction mixture was concentrated under reduced pressure to remove NH_3/MeOH, and added DCM (300 mL) (three times) was concentrated under reduced pressure to give N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (24 g, crude) as a yellow solid. MS (ESI) *m/z* 528.3 $[M+H]^+$

Step 11: 2-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001758] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (12 g, 22.73 mmol, 1 *eq*) in DCM (200 mL) was added Burgess reagent (11.91 g, 50.00 mmol, 2.2 *eq*). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (10 mL) at 20 °C, and then to remove solvent by N_2. The residue was purified by prep-HPLC (column: Phenomenex Titank C18 Bulk 250 * 100 mm 10u; mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 30% - 65%, 20min) to give 2-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (17 g, 99.29% purity) as a yellow solid. MS (ESI) *m/z* 510.3 $[M+H]^+$

Step 12: 2-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

Isomer 1:

[0001759] The desired compound was further separated by SFC (condition: column: REGIS (s,s) WHELK-O1 (250mm * 50mm, 10um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 60%-60%, 9.5min) to give 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (6.1 g, 11.96 mmol, 26.31% yield) as a yellow solid. MS (ESI) *m/z* 510.3 $[M+H]^+$

[0001760] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.64 - 11.51 (m, 1H), 8.98 - 8.86 (m, 1H), 7.70 - 7.38 (m, 2H), 7.32 - 7.21 (m, 1H), 7.16 - 6.69 (m, 2H), 5.08 - 4.47 (m, 2H), 3.88 - 3.76 (m, 1H), 3.70 - 3.60 (m, 1H), 3.27 - 2.93 (m, 2H), 2.35 (br s, 3H), 1.88 - 1.31 (m, 16H).

[0001761] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ = 11.28 - 11.09 (m, 1H), 8.82 - 8.62 (m, 1H), 7.73 - 7.52 (m, 1H), 7.37 - 7.22 (m, 2H), 7.20 - 6.96 (m, 2H), 5.08 - 4.86 (m, 1H), 4.70 - 4.46 (m, 1H), 3.88 - 3.78 (m, 1H), 3.70 - 3.51 (m, 1H), 3.14 - 3.09 (m, 2H), 2.40 - 2.13 (m, 3H), 1.87 - 1.37 (m, 16H).

[0001762] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.67 - 7.46 (m, 1H), 7.32 - 7.22 (m, 1H), 7.14 - 6.81 (m, 2H), 5.16 - 4.97 (m, 1H), 4.83 - 4.58 (m, 1H), 3.98 - 3.81 (m, 1H), 3.76 - 3.38 (m, 1H), 3.27 - 2.98 (m, 2H), 2.67 - 2.20 (m, 3H), 2.05 - 1.43 (m, 16H).

Isomer 2:

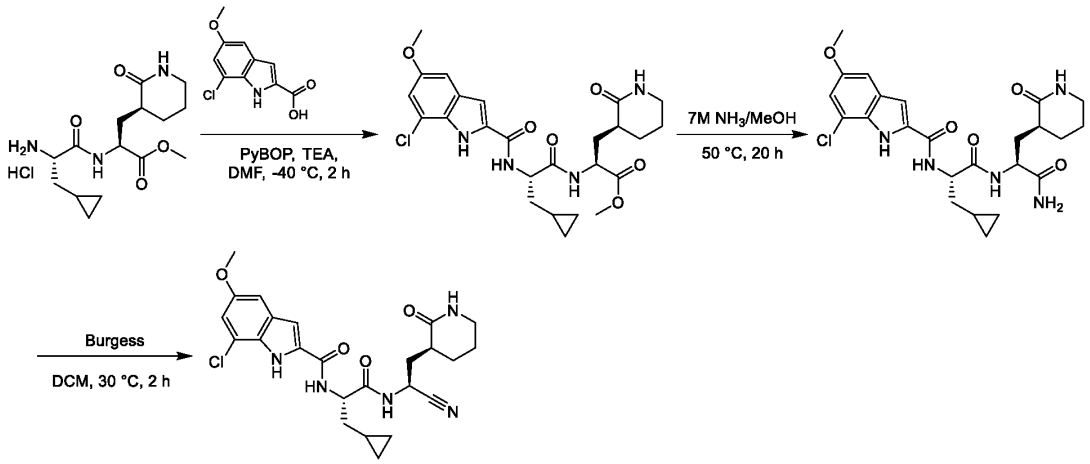
[0001763] 2-(7-Chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (7 g, 13.72 mmol, 30.20% yield) was obtained as a yellow solid. MS (ESI) *m/z* 510.3 $[M+H]^+$

[0001764] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.59 - 11.47 (m, 1H), 8.98 - 8.77 (m, 1H), 7.69 - 7.63 (m, 1H), 7.54 - 7.46 (m, 1H), 7.32 - 7.23 (m, 1H), 7.18 - 6.68 (m, 2H), 5.06 - 4.84 (m, 1H), 4.80 - 4.47 (m, 1H), 3.90 - 3.78 (m, 1H), 3.74 - 3.61 (m, 1H), 3.28 - 3.00 (m, 2H), 2.33 - 2.09 (m, 1H), 2.08 - 2.06 (m, 1H), 1.88 - 1.32 (m, 16H).

[0001765] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ = 11.26 - 11.02 (m, 1H), 8.74 - 8.57 (m, 1H), 7.76 - 7.51 (m, 1H), 7.32 - 7.21 (m, 2H), 7.17 - 6.93 (m, 2H), 5.07 - 4.87 (m, 1H), 4.73 - 4.51 (m, 1H), 3.87 - 3.79 (m, 1H), 3.73 - 3.52 (m, 1H), 3.08 (s, 2H), 2.29 - 2.12 (m, 3H), 1.86 - 1.38 (m, 16H).

[0001766] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.72 - 7.52 (m, 1H), 7.33 - 7.19 (m, 1H), 7.14 - 6.79 (m, 2H), 5.09 - 4.92 (m, 1H), 4.70 - 4.54 (m, 1H), 3.99 - 3.89 (m, 1H), 3.83 - 3.40 (m, 1H), 3.22 - 3.00 (m, 2H), 2.57 - 2.12 (m, 3H), 2.01 - 1.40 (m, 16H).

Example 219. Synthesis of viral protease inhibitor compound 900



Step 1: (S)-methyl2-((S)-2-(7-chloro-5-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001767] To a solution of 7-chloro-5-methoxy-1*H*-indole-2-carboxylic acid (1 g, 3.24 mmol, 85% purity, 1.1 *eq*, HCl) and methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl] propanoate (918.04 mg, 2.95 mmol, 1 *eq*) in DMF (15 mL) was added PyBOP (1.53 g, 2.95 mmol, 1 *eq*). TEA (895.02 mg, 8.85 mmol, 1.23 mL, 3 *eq*) in DMF (5 mL) was added, and then the mixture was stirred at -40 °C for 2 h. Upon completion, the mixture was quenched by water (60 mL) and was extracted with DCM (20 mL * 3), then was concentration in vacuum and was purified by column (SiO_2, petroleum ether: ethyl acetate= 5:1 to 0:1) to obtain (*S*)-methyl2-((*S*)-2-(7-chloro-5-methoxy-1*H*-indole- 2-carboxamido)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1.5 g, 2.02 mmol, 68.62% yield, 70% purity) as a brown gum. MS (ESI) *m/z* 519.2 $[M+H]^+$

Step 2: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-5-methoxy-1H-indole-2-carboxamide

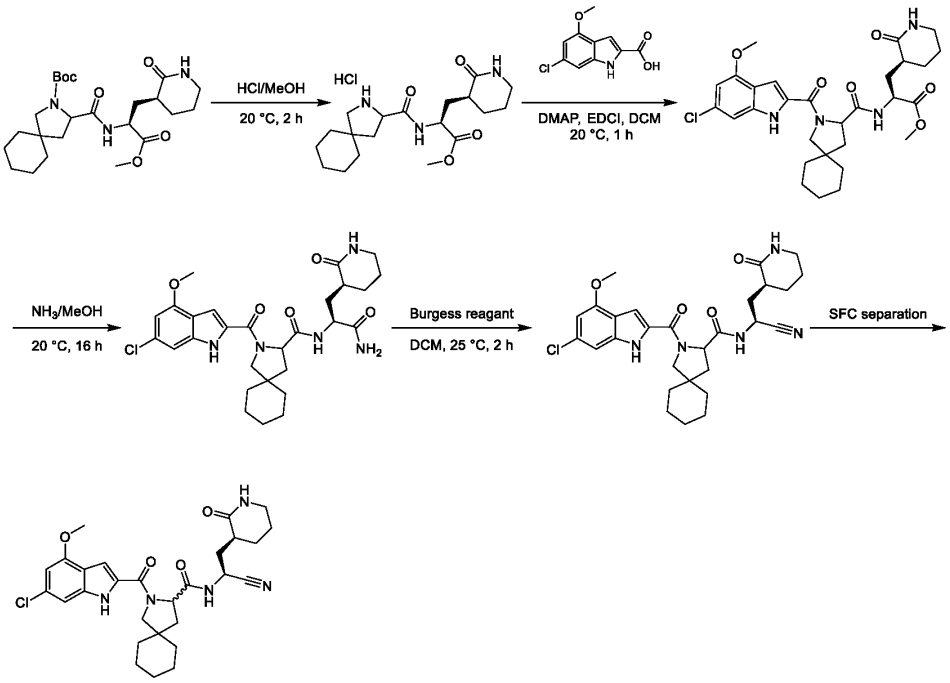
[0001768] A solution of (*S*)-methyl2-((*S*)-2-(7-chloro-5-methoxy-1*H*-indole-2-carboxamido)-3- cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (350 mg, 674.39 umol, 1 *eq*) in NH_3/MeOH (7M, 4 mL) was stirred at 50 °C for 20 h. Upon complteion, the mixture was concentrated in vacuum to obtain *N*-((*S*)-1-(((*S*)-1-amino-1 -oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-5-methoxy-1*H*-indole-2-carboxamide (1.3 g, crude) as a brown gum. MS (ESI) *m/z* 502.1 $[M-H]^+$

Step 3: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-methoxy-1H-indole-2-carboxamide

[0001769] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-1 -oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl) amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-5-methoxy-1*H*-indole-2-carboxamide (1.3 g, 2.58 mmol, 1 *eq*) in DCM (20 mL) was added Burgess reagent (1.84 g, 7.74 mmol, 3 *eq*) at 30 °C. The resulting mixture was stirred at 30 °C for 2 h. Upon completion, the mixture was quenched by water (2 mL) and was dried by blowing N_2. The mixture was purified by prep-HPLC (column: Waters Xbridge C18 150 * 50mm * 10um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 25%-55%, 10min) to obtain 7-chloro-*N*-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-methoxy-1*H*-indole-2-carboxamide (260 mg, 535.02 umol, 20.74% yield, 100% purity) as a white solid. MS (ESI) *m/z* 486.1$[M+H]^+$

[0001770] ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 11.57 (s, 1H), 8.99 (d, J = 8.0 Hz, 1H), 8.65 (d, J = 7.6 Hz, 1H), 7.53 (s, 1H), 7.15 (dd, J = 2.2, 11.3 Hz, 2H), 7.00 (d, J = 2.2 Hz, 1H), 5.07 (q, J = 8.0 Hz, 1H), 4.58 - 4.44 (m, 1H), 3.84 - 3.72 (m, 3H), 3.17 - 3.00 (m, 2H), 2.30 - 2.20 (m, 2H), 1.91 - 1.65 (m, 4H), 1.64 - 1.33 (m, 3H), 0.87 - 0.73 (m, 1H), 0.50 - 0.35 (m, 2H), 0.26 - 0.05 (m, 2H).

Example 220. Synthesis of viral protease inhibitor compound 908



Step 1: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoatemethyl

[0001771] A solution of tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (1.5 g, 3.22 mmol, 1 eq) in HCl/MeOH (15 mL) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to afford methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.25 g, crude, HCl) as a white solid. MS (ESI) m/z 366.2 $[M+H]^+$

Step 2: methyl (2S)-2-[[2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001772] To a solution of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.25 g, 3.10 mmol, 1 eq, HCl) and 6-chloro-4-methoxy-1H-indole-2-carboxylic acid (700 mg, 3.10 mmol, 1 eq) in DCM (40 mL) was added DMAP (1.14 g, 9.31 mmol, 3 eq). After adding EDCI (1.78 g, 9.31 mmol, 3 eq), the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (30mL), and then extracted with DCM (15 mL * 2). The combined organic layers were washed with HCl (1 M) (10 mL * 2), and then the

combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1 to 0/1, dichloromethane : methanol = 10:1, (UV 254 nm)) to give methyl (2S)-2-[[2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.2 g, 1.96 mmol, 63.24% yield, 93.7% purity) as a yellow solid. MS (ESI) m/z 573.2 $[M+H]^+$

Step 3: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001773] A solution of methyl (2S)-2-[[2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.1 g, 1.92 mmol, 1 eq) in NH_3/MeOH (7 M, 60 mL, 218.81 eq) was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove solvent to give N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.05 g, crude) as a yellow solid. MS (ESI) m/z 558.2 $[M+H]^+$

Step 4: 2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[0001774] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.04 g, 1.86 mmol, 1 eq) in DCM (20 mL) was added Burgess reagent (888.20 mg, 3.73 mmol, 2 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150*50mm* 10um; mobile phase: [water(10 mM NH_4HCO_3)-ACN];B%: 50%-70%, 10 min) to give 2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (500 mg, 886.03 umol, 47.54% yield, 95.7% purity) as a white solid. MS (ESI) m/z 540.2 $[M+H]^+$.

Step 5: 2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

Isomer 1:

[0001775] 2-(6-Chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (500 mg) was separated by SFC (column: REGIS (s,s) WHELK-O1 (250mm*30mm,5um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 50%-50%,6min) to give 2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (66.7 mg, 123.01 umol, 13.29% yield, 99.6% purity) as a white solid. MS (ESI) m/z 540.2 $[M+H]^+$.

[0001776] 1H NMR (400MHz, DMSO-d_6) δ = 11.76 - 11.61 (m, 1H), 8.88 (d, J = 8.4Hz, 1H), 7.67 - 7.33 (m, 1H), 7.14 - 6.86 (m, 2H), 6.67 - 6.48 (m, 1H), 5.06 - 4.87 (m, 1H), 4.49 (t, J = 8.8Hz, 1H), 3.92 (s, 2H), 3.88 - 3.80 (m, 1H), 3.66 (d, J = 10.3Hz, 1H), 3.33 (s, 6H), 2.38 - 2.17 (m, 2H), 2.03 - 0.83 (m, 14H)

[0001777] ^{1}H NMR (400MHz, DMSO-d_6, 273+80K) δ = 11.46 (s, 1H), 8.71 (s, 1H), 7.27 (s, 1H), 7.09 (s, 2H), 6.55 (s, 1H), 4.97 (s, 1H), 4.61 (s, 1H), 3.92 (s, 2H), 3.85 (d, J = 10.4Hz, 1H), 3.61 (s, 1H), 3.08 (s, 6H), 2.38 - 2.12 (m, 2H), 2.01 - 1.02 (m, 14H)

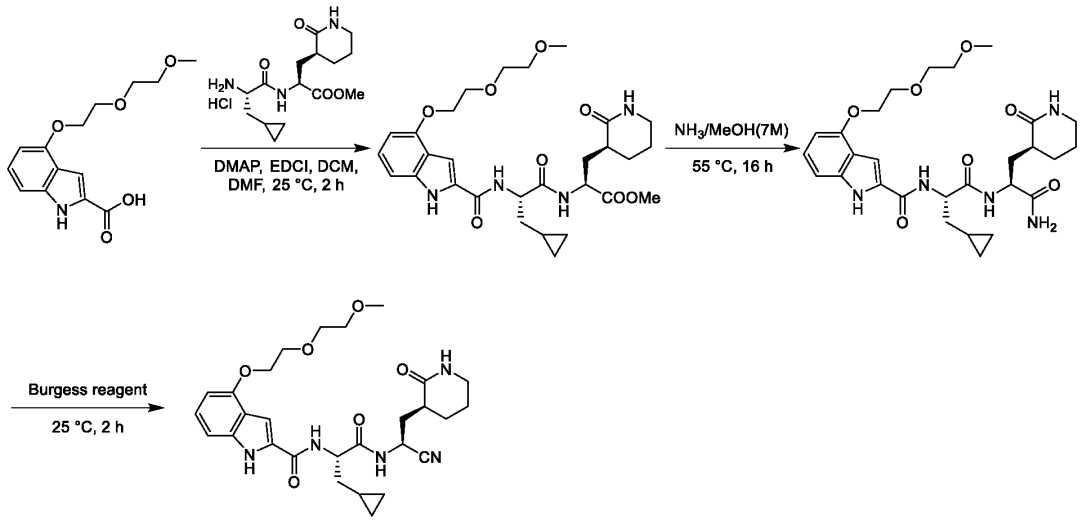
Isomer 2:

[0001778] 2-(6-Chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (111.6 mg, 206.65 umol, 22.32% yield, 100% purity) was obtained as a white solid. MS (ESI) m/z 540.2 $[M+H]^+$.

[0001779] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.76 - 11.64 (m, 1H), 8.81 (d, J = 8.4Hz, 1H), 7.53 - 7.41 (m, 1H), 7.06 (s, 1H), 6.97 (s, 1H), 6.65 - 6.51 (m, 1H), 5.04 - 4.86 (m, 1H), 4.58 - 4.38 (m, 1H), 3.92 (s, 2H), 3.84 (d, J = 9.8Hz, 1H), 3.76 - 3.57 (m, 1H), 3.33 (s, 6H), 2.24 - 2.11 (m, 2H), 1.88 - 1.10 (m, 14H)

[0001780] 1H NMR (400MHz, DMSO-d_6, 273+80K) δ = 11.48 (s, 1H), 8.64 (s, 1H), 7.23 (s, 1H), 7.09 (s, 1H), 6.93 (s, 1H), 6.56 (s, 1H), 4.97 (s, 1H), 4.59 (s, 1H), 3.93 (s, 2H), 3.85 (d, J = 10.8Hz, 1H), 3.65 (s, 1H), 3.08 (s, 6H), 2.20 (s, 2H), 2.01 - 1.23 (m, 14H)

Example 221. Synthesis of viral protease inhibitor compound 1057



Step 1: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[[4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carbonyl]amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001781] To a mixture of 4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxylic acid (500 mg, 1.79 mmol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (684.99 mg, 1.97 mmol, 1.1 eq, HCl) in DCM (9 mL) and DMF (3 mL) was added DMAP (656.15 mg, 5.37 mmol, 3 eq) and EDCI (686.39 mg, 3.58 mmol, 2 eq) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL * 3). The combined organic layers were washed with brine (15 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3/1 to 0/1) to give methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[[4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carbonyl]amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (850 mg, 1.48 mmol, 82.91% yield) as a yellow solid. MS (ESI) *m/z* 573.3 $[M+H]^+$

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide

[0001782] A mixture of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[[4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carbonyl]amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (850 mg, 1.41 mmol, 95% purity, 1 *eq*) in NH_3 /MeOH (7 M, 25 mL, 124.10 *eq*) was stirred at 55 °C for 16 hours. Upon completion, the reaction mixture

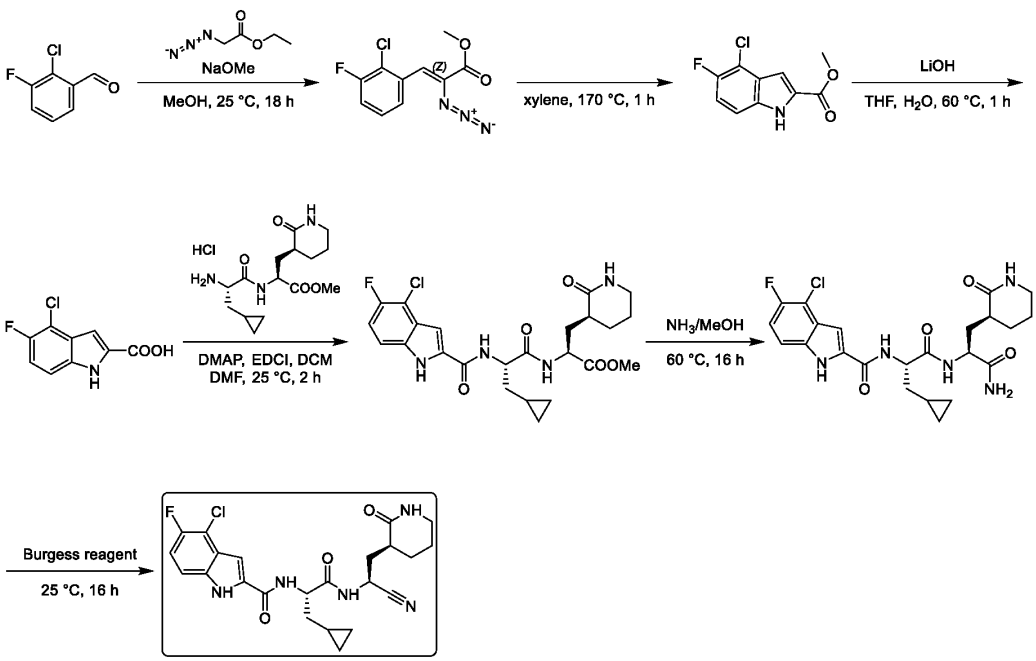
was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide (781 mg, 1.22 mmol, 86.41% yield, 87% purity) as a yellow solid. MS (ESI) *m/z* 558.3 $[M+H]^+$

Step 3: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide

[0001783] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide (730 mg, 1.14 mmol, 87% purity, 1 eq) in DCM (10 mL) was added Burgess reagent (542.82 mg, 2.28 mmol, 2 eq) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water(10 mM NH4HCO3)-ACN];B%: 20%-50%, 8min) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-[2-(2-methoxyethoxy)ethoxy]-1H-indole-2-carboxamide (230 mg, 426.22 umol, 37.42% yield) as a white solid. MS (ESI) *m/z* 540.2 $[M+H]^+$

[0001784] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.56 (s, 1H), 8.89 (d, *J*=8.2 Hz, 1H), 8.58 (d, *J*=7.5 Hz, 1H), 7.52 (br s, 1H), 7.39 (d, *J*=1.5 Hz, 1H), 7.11 - 6.99 (m, 2H), 6.50 (d, *J*=7.5 Hz, 1H), 5.10 - 5.01 (m, 1H), 4.49 - 4.41 (m, 1H), 4.21 (t, *J*=4.4 Hz, 2H), 3.86 - 3.79 (m, 2H), 3.63 (dd, *J*=3.7, 5.7 Hz, 2H), 3.49 (dd, *J*=3.7, 5.5 Hz, 2H), 3.26 (s, 3H), 3.13 - 3.03 (m, 2H), 2.36 - 2.20 (m, 2H), 1.90 - 1.76 (m, 3H), 1.75 - 1.65 (m, 1H), 1.62 - 1.50 (m, 1H), 1.49 - 1.34 (m, 2H), 0.88 - 0.75 (m, 1H), 0.48 - 0.33 (m, 2H), 0.24 - 0.07 (m, 2H)

Example 221a. Synthesis of viral protease inhibitor compound 822



Step 1: methyl (Z)-2-azido-3-(2-chloro-3-fluoro-phenyl)prop-2-enoate

[0001785] A mixture of NaOMe (3.41 g, 63.07 mmol, 2 *eq*) in MeOH (30 mL) was cooled to -10 °C, a mixture of 2-chloro-3-fluoro-benzaldehyde (5 g, 31.53 mmol, 1 *eq*) and ethyl 2-azidoacetate (8.14 g, 63.07 mmol, 7.21 mL, 2 *eq*) in MeOH (100 mL) was added drop-wise to the former solution, the mixture was stirred at 25 °C for 18 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue, the residue was diluted with H2O 60 mL and extracted with EA 90 mL (30 mL * 3). The combined organic layers were washed with brine 45 mL (45 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=1/0) to give methyl (Z)-2-azido-3-(2-chloro-3-fluoro-phenyl)prop-2-enoate (2.5 g, 9.78 mmol, 31.01% yield) as a yellow solid.

Step 2: methyl 4-chloro-5-fluoro-1H-indole-2-carboxylate

[0001786] A mixture of methyl (Z)-2-azido-3-(2-chloro-3-fluoro-phenyl)prop-2-enoate (2.3 g, 9.00 mmol, 1 *eq*) in xylene (25 mL) was stirred at 170 °C for 1 h. Upon completion, the reaction mixture was filtered to give methyl 4-chloro-5-fluoro-1H-indole-2-carboxylate (1.4 g, 6.15 mmol, 68.36% yield) as a white solid.

Step 3: 4-chloro-5-fluoro-1H-indole-2-carboxylic acid

[0001787] A mixture of methyl 4-chloro-5-fluoro-1H-indole-2-carboxylate (1.4 g, 6.15 mmol, 1 *eq*) in THF (7 mL) and H_2O (7 mL) was added $LiOH.H_2O$ (516.20 mg, 12.30 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 60 °C for 1 hour. Upon completion, the reaction mixture was adjusted to acidty by 1M HCl solution, and extracted with EA 45 mL (15 mL * 3). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na2SO4, filtered and concentrated under reduced pressure to give 4-chloro-5-fluoro-1H-indole-2-carboxylic acid (1 g, 4.68 mmol, 76.12% yield) as a white solid. (ESI) *m/z* 211.9 $[M-H]^+$

Step 4: methyl (2S)-2-[[(2S)-2-[(4-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001788] To a mixture of 4-chloro-5-fluoro-1H-indole-2-carboxylic acid (500 mg, 2.34 mmol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (895.68 mg, 2.57 mmol, 1.1 eq, HCl) in DCM (10 mL) and DMF (3 mL) was added DMAP (857.96 mg, 7.02 mmol, 3 eq) and EDCI (897.50 mg, 4.68 mmol, 2 eq) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was diluted with H2O 30 mL and extracted with EA 60 mL (20 mL * 3). The combined organic layers were washed with brine 30 mL (30 mL * 1), dried over Na2SO4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=5/1 to 0/1) to give methyl (2S)-2-[[(2S)-2-[(4-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (800 mg, 1.58 mmol, 67.41% yield) as a white solid. MS (ESI) *m/z* 505.0 $[M-H]^+$

Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-5-fluoro-1H-indole-2-carboxamide

[0001789] A mixture of methyl (2S)-2-[[(2S)-2-[(4-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (800 mg, 1.58 mmol, 1 *eq*) in NH_3/MeOH (7 M, 20 mL, 88.72 *eq*) was stirred at 60 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-

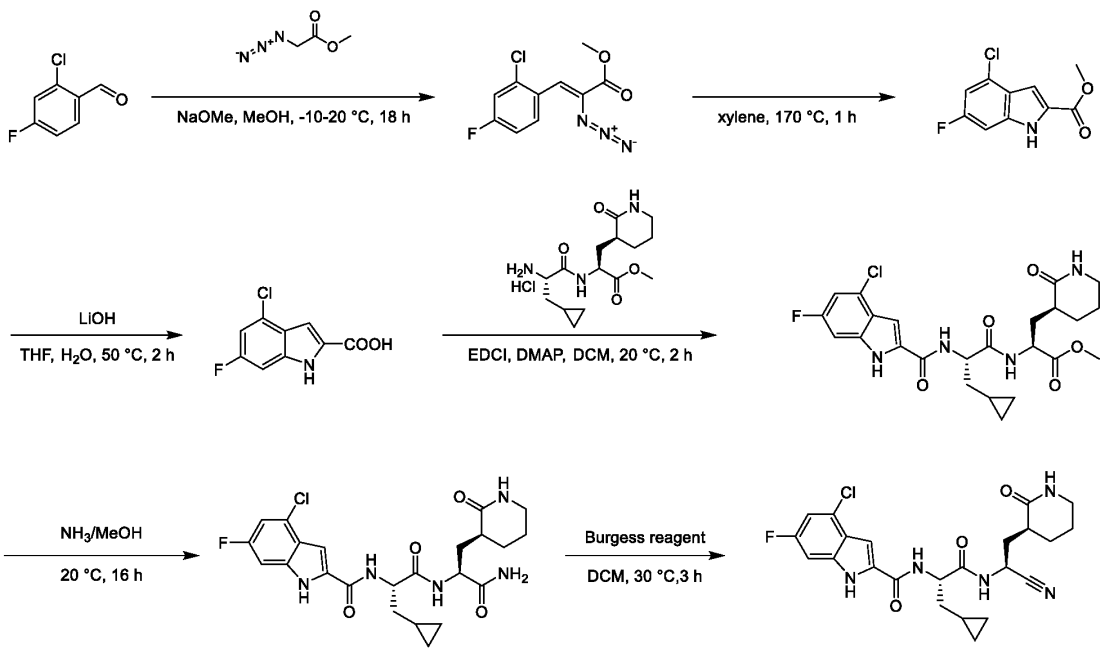
(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-5-fluoro-1H-indole-2-carboxamide (730 mg, 1.35 mmol, 85.57% yield, 91% purity) as a white solid. MS (ESI) *m/z* 492.2 $[M+H]^+$

Step 6: 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide

[0001790] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-5-fluoro-1H-indole-2-carboxamide (730 mg, 1.26 mmol, 85% purity, 1 *eq*) in DCM (20 mL) was added Burgess reagent (1.05 g, 4.41 mmol, 3.5 eq) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude. The crude was purified by prep-HPLC (neutral condition; column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 25%-55%,8min) to give 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide (300 mg, 633.01 umol, 50.19% yield) as a white solid. MS (ESI) *m/z* 474.1 [M+H]

[0001791] ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.06 (br s, 1H), 8.94 (d, *J*=8.2 Hz, 1H), 8.81 (d, *J*=7.5 Hz, 1H), 7.54 (br s, 1H), 7.47 (s, 1H), 7.40 (dd, *J*=4.0, 9.0 Hz, 1H), 7.23 (t, *J*=9.4 Hz, 1H), 5.11 - 5.03 (m, 1H), 4.51 - 4.42 (m, 1H), 3.09 (br s, 2H), 2.31 - 2.20 (m, 2H), 1.92 - 1.76 (m, 3H), 1.76 - 1.64 (m, 1H), 1.56 (br d, *J*=3.3 Hz, 1H), 1.51 - 1.33 (m, 2H), 0.88 - 0.76 (m, 1H), 0.49 - 0.35 (m, 2H), 0.26 - 0.05 (m, 2H)

Example 222. Synthesis of viral protease inhibitor compound 824



[0001792] Step 1: (Z)-methyl 2-azido-3-(2-chloro-4-fluorophenyl)acrylate

[0001793] To a solution of NaOMe (13.63 g, 252.27 mmol, 4 eq) in MeOH (50 mL), then 2-chloro-4-fluoro-benzaldehyde (10 g, 63.07 mmol, 1 eq) and methyl 2-azidoacetate (30.49 g, 264.89 mmol, 4.2 eq) in MeOH (50 mL) was added at -10 °C. The mixture was stirred at 20 °C for 18 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give methyl (Z)-2-azido-3-(2-chloro-4-fluoro-phenyl)prop-2-enoate (7 g, crude) as a yellow solid.

[0001794] Step 2: methyl 4-chloro-6-fluoro-1H-indole-2-carboxylate

[0001795] To a solution of methyl (Z)-2-azido-3-(2-chloro-4-fluoro-phenyl)prop-2-enoate (6 g, 23.47 mmol, 1 eq) in XYLENE (70 mL). The mixture was stirred at 170 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 8/1) to give methyl 4-chloro-6-fluoro-1H-indole-2-carboxylate (2 g, 8.79 mmol, 37.44% yield) as a yellow solid. MS (ESI) m/z 228.1 $[M+H]^+$.

[0001796] Step 3: 4-chloro-6-fluoro-1H-indole-2-carboxylic acid

[0001797] To a solution of methyl 4-chloro-6-fluoro-1H-indole-2-carboxylate (2 g, 8.79 mmol, 1 eq) in THF (20 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (1.11 g, 26.36 mmol, 3 eq). The mixture was stirred at 50 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. Then 1M HCl was added, adjust pH = 3, then was filtered and concentrated under reduced pressure to give 4-chloro-6-fluoro-1H-indole-2-carboxylic acid (1.6 g, crude) as a yellow solid. MS (ESI) m/z 214.0 $[M+H]^+$.

[0001798] Step 4: (S)-methyl 2-((S)-2-(4-chloro-6-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001799] To a solution of 4-chloro-6-fluoro-1H-indole-2-carboxylic acid (1 g, 4.68 mmol, 1 eq), methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.63 g, 4.68 mmol, 1 eq, HCl), DMAP (1.72 g, 14.05 mmol, 3 eq) in DCM (10 mL), then EDCI (1.80 g, 9.36 mmol, 2 eq) was added. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O 35 mL at 20 °C, and then extracted with DCM (35 mL * 3). The combined organic layers were washed with 1M HCl (40 mL * 2), then the combined organic layers were washed with brine (40 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 0/1) to give methyl (2S)-2-[[(2S)-2-[(4-chloro-6-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.1 g, 2.17 mmol, 46.35% yield, 100% purity) as a yellow solid. MS (ESI) m/z 507.2 $[M+H]^+$.

[0001800] Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-chloro-6-fluoro-1H-indole-2-carboxamide

[0001801] To a solution of methyl (2S)-2-[[(2S)-2-[(4-chloro-6-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.06 g, 2.09 mmol, 1 eq) in NH_3/MeOH (7 M, 20 mL, 66.96 eq). The mixture was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-

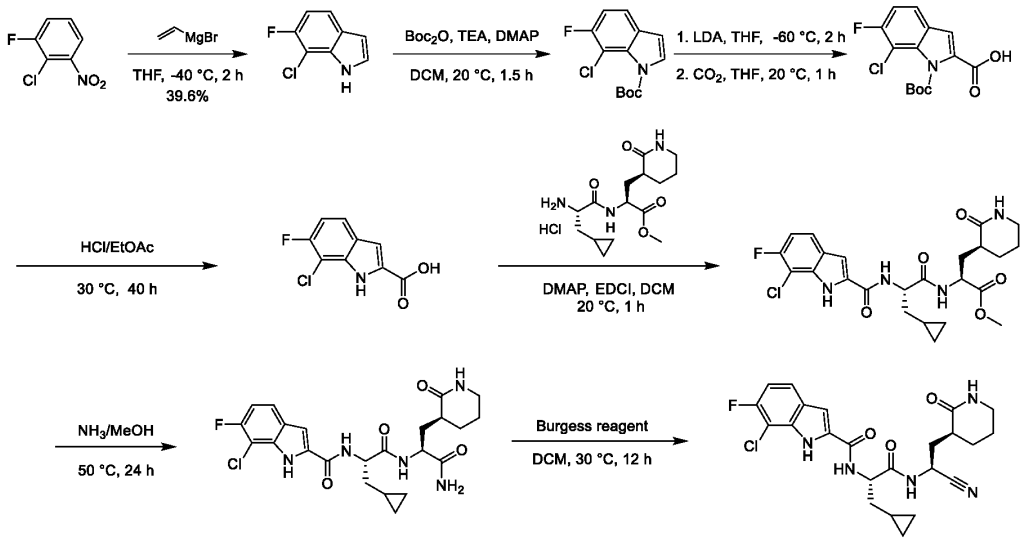
piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-6-fluoro-1H-indole-2-carboxamide (1 g, crude) as a yellow solid. MS (ESI) m/z 492.2 $[M+H]^+$.

[0001802] Step 6: 4-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-fluoro-1H-indole-2-carboxamide

[0001803] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-6-fluoro-1H-indole-2-carboxamide (980 mg, 1.99 mmol, 1 eq) in DCM (10 mL) was added BURGESS REAGENT (949.46 mg, 3.98 mmol, 2 eq). The mixture was stirred at 30 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150 *50mm *10um; mobile phase: [water(10mM NH4HCO3)-ACN];B%: 35%-60%,10min) to give 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-fluoro-1H-indole-2-carboxamide (375 mg, 791.26 umol, 39.72% yield, 100% purity) as a white solid. MS (ESI) m/z 474.1 $[M+H]^+$.

[0001804] ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.04 (s, 1H), 8.94 (d, J=8.1 Hz, 1H), 8.77 (d, J=7.5 Hz, 1H), 7.53 (s, 1H), 7.45 (s, 1H), 7.15 (d, J=9.4 Hz, 2H), 5.07 (d, J=7.9 Hz, 1H), 4.46 (d, J=5.7 Hz, 1H), 3.16 - 2.98 (m, 2H), 2.26 (d, J=9.0 Hz, 2H), 1.97 - 1.63 (m, 4H), 1.46 (s, 3H), 0.81 (dd, J=5.7, 7.7 Hz, 1H), 0.41 (dd, J=3.5, 7.5 Hz, 2H), 0.26 - 0.03 (m, 2H).

Example 223. Synthesis of viral protease inhibitor compound 828



[0001805] Step 1: 7-chloro-6-fluoro-1H-indole

[0001806] To a mixture of 2-chloro-1-fluoro-3-nitro-benzene (10 g, 56.97 mmol, 1 eq) in THF (100 mL) was added bromo(vinyl)magnesium (1 M, 199.38 mL, 3.5 eq) drop-wise at -40 °C under N_2. The mixture was stirred at -40 °C for 2 h under N_2. Upon completion, the reaction was quenched by addition NH_4Cl (500 mL) and then extracted with EtOAc (300 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by column chromatography (SiO_2, EtOAc:MEOH = 10:1) to give product 7-chloro-6-fluoro-1H-indole (4.8 g, 25.47 mmol, 44.72% yield, 90% purity) as yellow oil. MS (ESI) m/z 170.0 $[M+H]^+$

[0001807] Step 2: tert-butyl 7-chloro-6-fluoro-indole-1-carboxylate

[0001808] To a mixture of 7-chloro-6-fluoro-1H-indole (4.8 g, 28.30 mmol, 1 eq) in DCM (50 mL) was added Boc_2O (6.80 g, 31.14 mmol, 7.15 mL, 1.1 eq), TEA (3.44 g, 33.97 mmol, 4.73 mL, 1.2 eq) and DMAP (691.60 mg, 5.66 mmol, 0.2 eq) at 20 °C under N_2. The mixture was stirred at 20 °C for 1.5 h. Upon completion, the reaction mixture was poured into water (50 mL) and extracted with DCM (40 mL * 2). The combined organic layers were concentrated under reduced pressure and was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 20/1) to give product tert-butyl 7-chloro-6-fluoro-indole-1-carboxylate (6 g, 22.25 mmol, 78.60% yield) as white solid. MS (ESI) m/z 270.0 $[M+H]^+$

[0001809] Step 3: 1-tert-butoxycarbonyl-7-chloro-6-fluoro-indole-2-carboxylic acid

[0001810] To a mixture of tert-butyl 7-chloro-6-fluoro-indole-1-carboxylate (2.3 g, 8.53 mmol, 1 eq) in THF (25 mL) was added LDA (2M, 7.25 mL, 1.7 eq) at -60 °C under N_2. The mixture was stirred at -60 °C for 2 h, then the above solution wasadded into drikold (18.77 g, 426.50 mmol, 50 eq) and let stand for 1 h at 20 °C. Upon completion, the reaction mixture was poured into water (100 mL) under N_2 and stirred for 10 min. The aqueous phase was added 1 M HCl to pH~3-4 at 0 °C and extracted with ethyl acetate (50 mL * 3). The combined organic phase was washed with brine (80 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. It was triturated with Petroleum ether:Ethyl acetate = 50:1 (100 mL) to give product 1-tert-butoxycarbonyl-7-chloro-6-fluoro-indole-2-carboxylic acid (1.5 g, 4.78 mmol, 56.06% yield) as white powder. MS (ESI) m/z 314.0 $[M+H]^+$

[0001811] Step 4: 7-chloro-6-fluoro-1H-indole-2-carboxylic acid

[0001812] A solution of 1-tert-butoxycarbonyl-7-chloro-6-fluoro-indole-2-carboxylic acid (4.3 g, 13.71 mmol, 1 eq) in HCl/EtOAc (4 M, 50 mL, 14.59 eq) was stirred at 30 °C for 40 h. Upon completion, the reaction mixture was concentrated under pressure reduced to get the crude product 7-chloro-6-fluoro-1H-indole-2-carboxylic acid (2.9 g, crude) as white solid. MS (ESI) m/z 212.0 $[M+H]^+$

[0001813] Step 5: methyl (2S)-2-[[(2S)-2-[(7-chloro-6-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001814] To a solution of 7-chloro-6-fluoro-1H-indole-2-carboxylic acid (0.7 g, 3.28 mmol, 1.5 eq) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (759.97 mg, 2.18 mmol, 1 eq, HCl) in DCM (7 mL) was added EDCI (837.67 mg, 4.37 mmol, 2 eq), DMAP (800.77 mg, 6.55 mmol, 3 eq). The solution was stirred at 20 °C, for 1 h. Upon completion, the mixture was quenched by addition H_2O (40 mL) and extracted with DCM (10 mL * 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/1 to 0/1 and then DCM:MeOH = 5:1) to give product methyl (2S)-2-[[(2S)-2-[(7-chloro-6-fluoro-1H-

indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.8 g, 1.50 mmol, 68.62% yield, 95% purity) as yellow solid. MS (ESI) m/z 505.1 $[M+H]^+$

[0001815] Step 6: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-6-fluoro-1H-indole-2-carboxamide

[0001816] The methyl (2S)-2-[[(2S)-2-[(7-chloro-6-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.78 g, 1.54 mmol, 1 eq) in NH_3/MEOH (15 mL) was stirred at 50 °C for 24 h. Upon completion, the reaction mixture was concentrated under pressure reduced to give the product N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-6-fluoro-1H-indole-2-carboxamide (0.75 g, crude) as white solid. MS (ESI) m/z 492.2 $[M+H]^+$

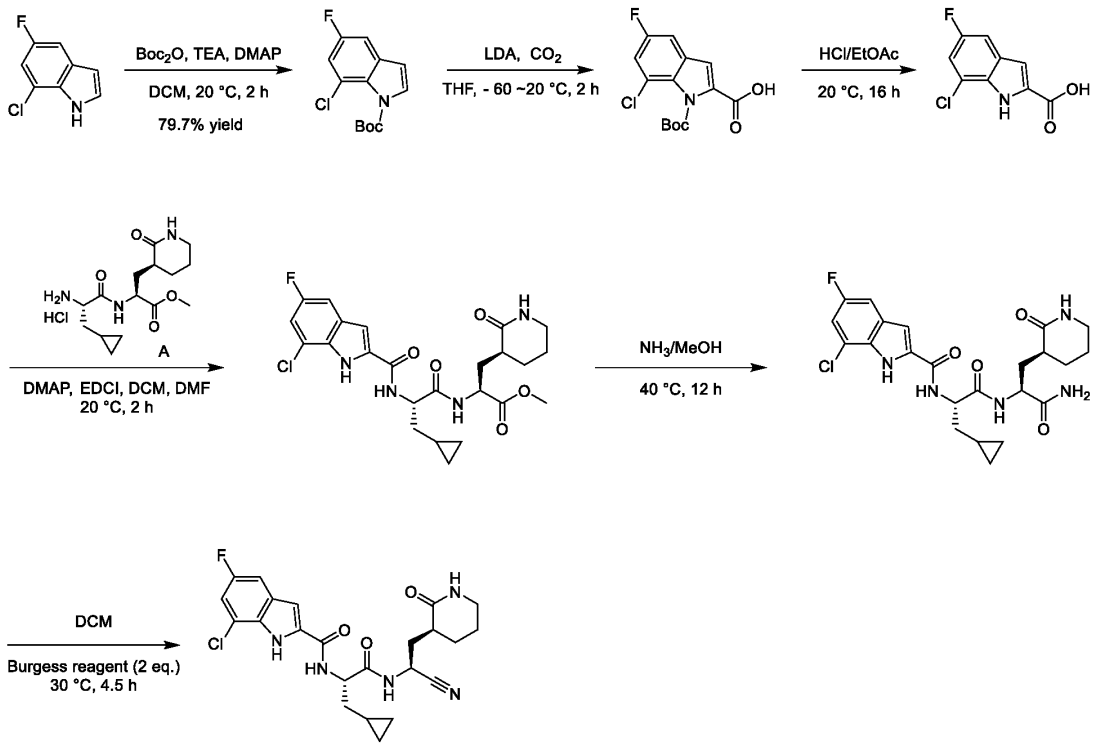
[0001817] Step 7: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-fluoro-1H-indole-2-carboxamide

[0001818] The N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-6-fluoro-1H-indole-2-carboxamide (0.7 g, 1.31 mmol, 92% purity, 1 eq) in DCM (10 mL) was add BURGESS REAGENT (935.91 mg, 3.93 mmol, 3 eq). The mixture was stirred at 30 °C for 12 h. Upon completion, the reaction was quenched with water (2 mL) and blow-dried with N_2 and was purified by prep-HPLC (column: Waters Xbridge C18 150*50mm* 10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-55%,10min) to give product 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-fluoro-1H-indole-2-carboxamide (0.23 g, 480.45 umol, 36.70% yield, 99% purity) as white solid. MS (ESI) m/z 474.1 $[M+H]^+$

[0001819] ^1H NMR (400 MHz, DMSO-d_6) δ = 8.99 (d, J = 7.9 Hz, 1H), 8.68 (d, J = 7.5 Hz, 1H), 7.66 (dd, J = 4.9, 8.7 Hz, 1H), 7.53 (br s, 1H), 7.29 (s, 1H), 7.18 - 7.07 (m, 1H), 5.07

(q, J = 7.9 Hz, 1H), 4.59 - 4.42 (m, 1H), 3.18 - 3.04 (m, 2H), 2.32 - 2.18 (m, 2H), 2.07 (s, 1H), 1.93 - 1.76 (m, 3H), 1.71 (dt, J = 4.0, 8.9 Hz, 1H), 1.63 - 1.34 (m, 3H), 0.89 - 0.74 (m, 1H), 0.53 - 0.36 (m, 2H), 0.24 - 0.16 (m, 1H), 0.15 - 0.06 (m, 1H).

Example 224. Synthesis of viral protease inhibitor compound 830



[0001820] Step 1: tert-butyl 7-chloro-5-fluoro-1H-indole-1-carboxylate

[0001821] To a solution of 7-chloro-5-fluoro-1H-indole (4.5 g, 26.54 mmol, 1 eq) and TEA (3.22 g, 31.84 mmol, 4.43 mL, 1.2 eq) in DCM (20 mL) was added DMAP (648.36 mg, 5.31 mmol, 0.2 eq) and Boc_2O (6.37 g, 29.19 mmol, 6.71 mL, 1.1 eq) under N_2, then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 100 mL, and then extracted with DCM 150 ml (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 15:1) to give the product tert-butyl 7-chloro-5-fluoro-indole-1-carboxylate (6 g, 21.13 mmol, 79.65% yield, 95% purity) as a yellow oil.

[0001822] Step 2: 1-(tert-butoxycarbonyl)-7-chloro-5-fluoro-1H-indole-2-carboxylic acid

[0001823] To a mixture of tert-butyl 7-chloro-5-fluoro-indole-1-carboxylate (3 g, 11.12 mmol, 1 eq) in THF (40 mL) was added LDA (2 M, 7.23 mL, 1.3 eq) at -60 °C under N_2. The mixture was stirred at -60 °C for 1.5 h, then the above solution was added into drikold (24.48 g, 556.18 mmol, 50 eq) and let stand for 0.5 h at 20 °C. Upon completion, the reaction mixture was poured into ice-water (100 mL) under N_2 and stirred for 10 min. The aqueous phase was added 1 M HCl to pH ~ 3-4 at 0 °C and extracted with ethyl acetate (60 mL * 3). The combined organic phase was washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC to give the product 1-tert-butoxycarbonyl-7-chloro-5-fluoro-indole-2-carboxylic acid (1.8 g, 5.74 mmol, 51.58% yield, N/A purity) as a white solid.

[0001824] Step 3: 7-chloro-5-fluoro-1H-indole-2-carboxylic acid

[0001825] To a solution of 1-tert-butoxycarbonyl-7-chloro-5-fluoro-indole-2-carboxylic acid (1 g, 3.19 mmol, 1 eq) in HCl/EtOAc (4 M, 40.00 mL, 50.19 eq), and then the mixture was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product 7-chloro-5-fluoro-1H-indole-2-carboxylic acid (660 mg, crude, HCl) as a yellow solid.

[0001826] Step 4: (S)-methyl 2-((S)-2-(7-chloro-5-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001827] To a solution of 7-chloro-5-fluoro-1H-indole-2-carboxylic acid (660 mg, 2.64 mmol, 1 eq, HCl) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.07 g, 3.43 mmol, 1.3 eq) in DMF (5 mL) and DCM (20 mL), and then DMAP (967.38 mg, 7.92 mmol, 3 eq) and EDCI (1.01 g, 5.28 mmol, 2 eq) was added, then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM 150 mL (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate=5:1 to 0:1) to give the product methyl (2S)-2-[[(2S)-2-[(7-chloro-5-

fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (770 mg, 1.41 mmol, 53.52% yield, 93% purity) as a yellow solid. MS (ESI) m/z 507.2 $[M+H]^+$.

[0001828] Step 5: (S)-methyl 2-((S)-2-(7-chloro-5-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001829] To a solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (770 mg, 1.52 mmol, 1 eq) in NH3/MeOH (7 M, 40.00 mL, 184.35 eq), and then the mixture was stirred at 40 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-5-fluoro-1H-indole-2-carboxamide (720 mg, crude) as a yellow solid. MS (ESI) m/z 492.2 $[M+H]^+$.

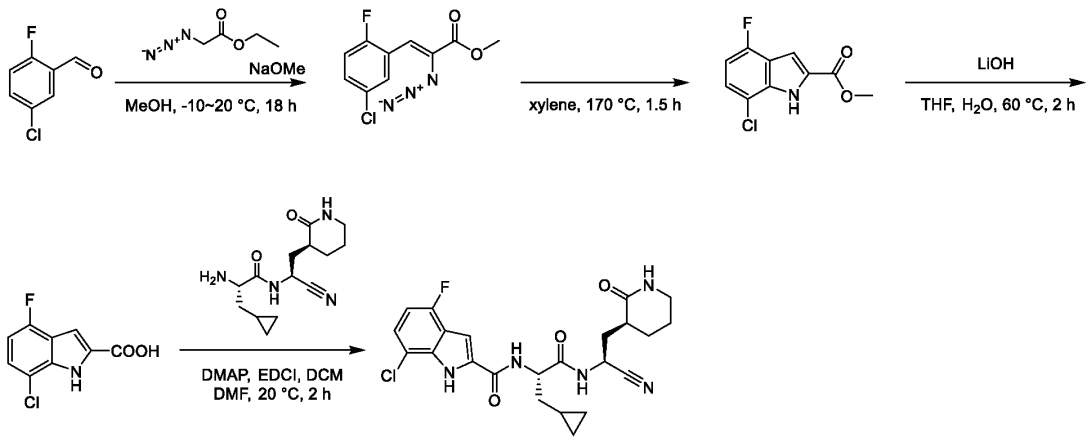
[0001830] Step 6: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-fluoro-1H-indole-2-carboxamide

[0001831] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-5-fluoro-1H-indole-2-carboxamide (660 mg, 1.34 mmol, 1 eq) in DCM (15 mL) and BURGESS REAGENT (639.44 mg, 2.68 mmol, 2 eq) was added, and then the mixture was stirred at 30 °C for 4.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150 * 50mm * 10um; mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 10min) to give the product 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide (232.57 mg, 490.73 umol, 36.58% yield, 100% purity) as a white solid. MS (ESI) m/z 474.2 $[M+H]^+$.

[0001832] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.87 (s, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.74 (br d, J = 7.6 Hz, 1H), 7.53 (br s, 1H), 7.47 (dd, J = 2.2, 9.3 Hz, 1H), 7.33 (dd, J = 2.2, 9.3 Hz, 1H), 7.26 (s, 1H), 5.07 (br d, J = 7.8 Hz, 1H), 4.51 (s, 1H), 3.15 - 3.04 (m, 2H), 2.25

(br t, J = 8.7 Hz, 2H), 1.88 - 1.75 (m, 3H), 1.74 - 1.67 (m, 1H), 1.39 - 1.57 (s, 3H), 0.86 - 0.76 (m, 1H), 0.48 - 0.37 (m, 2H), 0.23 - 0.07 (m, 2H)

Example 225. Synthesis of viral protease inhibitor compound 832



[0001833] Step 1: (Z)-methyl 2-azido-3-(5-chloro-2-fluorophenyl)acrylate

[0001834] To a solution of NaOMe (3.41 g, 63.06 mmol, 2 eq) in MeOH (50 mL), then 5-chloro-2-fluoro-benzaldehyde (5 g, 31.53 mmol, 1 eq) and ethyl 2-azidoacetate (8.14 g, 63.06 mmol, 7.21 mL, 2 eq) in MeOH (50 mL) was added at -10 °C. The mixture was stirred at 20 °C for 18 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM 150 mL (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 5:1) to give the product methyl (Z)-2-azido-3-(5-chloro-2-fluoro-phenyl)prop-2-enoate (3.7 g, 13.75 mmol, 43.61% yield, 95% purity) as a white solid.

[0001835] Step 2: methyl 7-chloro-4-fluoro-1H-indole-2-carboxylate

[0001836] To a solution of methyl (Z)-2-azido-3-(5-chloro-2-fluoro-phenyl)prop-2-enoate (3.7 g, 14.47 mmol, 1 eq) in XYLENE (40 mL) and the mixture was stirred at 170 °C for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with PE:EA = 20:1 (100 mL) at 20 °C for 10

min to give the product methyl 7-chloro-4-fluoro-1H-indole-2-carboxylate (1.6 g, 6.68 mmol, 46.14% yield, 95% purity) as a white solid. MS (ESI) m/z 228.1 $[M+H]^+$.

[0001837] Step 3: 7-chloro-4-fluoro-1H-indole-2-carboxylic acid

[0001838] To a solution of methyl 7-chloro-4-fluoro-1H-indole-2-carboxylate (1.5 g, 6.59 mmol, 1 eq) THF (10 mL) and H_2O (5 mL), then LiOH (315.64 mg, 13.18 mmol, 2 eq) was added, and the mixture was stirred at 60 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 100 mL at 0 °C, and then HCl (1 M) was added dropwise to pH to 3~4, and extracted with EA (50 mL * 3). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the product 7-chloro-4-fluoro-1H-indole-2-carboxylic acid (1.4 g, crude) as a white solid.

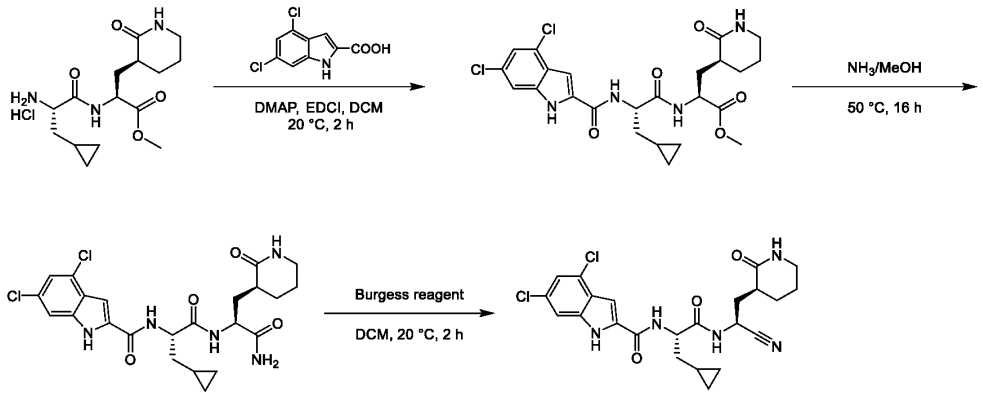
[0001839] Step 4: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-fluoro-1H-indole-2-carboxamide

[0001840] To a solution of 7-chloro-4-fluoro-1H-indole-2-carboxylic acid (100 mg, 468.18 umol, 1.30 eq) and (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-cyclopropyl-propanamide (200 mg, 359.26 umol, 50% purity, 1 eq) in DMF (2 mL) and DCM (5 mL), and then DMAP (131.67 mg, 1.08 mmol, 3 eq) and EDCI (137.74 mg, 718.52 umol, 2 eq) was added, then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM 150 mL (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30mm * 10um; mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 30%-50%, 8 min) to give the product 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-fluoro-1H-indole-2-carboxamide (112.98 mg, 238.39 umol, 66.36% yield, 100% purity) as a white solid. MS (ESI) m/z 474.2 $[M+H]^+$.

[0001841] ^1H NMR (400 MHz, DMSO-d_6) δ = 12.12 (br s, 1H), 9.10 - 8.97 (m, 1H), 8.79 (d, J = 7.2 Hz, 1H), 7.55 (br s, 1H), 7.36 - 7.33 (m, 1H), 7.33 - 7.26 (m, 1H), 6.90 (dd, J =

8.6, 9.6 Hz, 1H), 5.13 - 4.98 (m, 1H), 4.58 - 4.47 (m, 1H), 3.14 - 3.03 (m, 2H), 2.30 - 2.17 (m, 2H), 1.88 - 1.67 (m, 4H), 1.61 - 1.38 (m, 3H), 0.86 - 0.77 (m, 1H), 0.48 - 0.38 (m, 2H), 0.24 - 0.18 (m, 1H), 0.14 - 0.08 (m, 1H)

Example 226. Synthesis of viral protease inhibitor compound 840



[0001842] Step 1: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,6-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001843] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 2.87 mmol, 1 eq, HCl) and 4,6-dichloro-1H-indole-2-carboxylic acid (661.37 mg, 2.87 mmol, 1 eq) in DCM (40 mL), then DMAP (1.05 g, 8.62 mmol, 3 eq) was added, and then EDCI (1.65 g, 8.62 mmol, 3 eq) was added. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 30 mL, and then extracted with DCM 40 mL (20 mL * 2). The combined organic layers were washed with HCl (1 M) 30 mL (15 mL * 2), the combined organic layers were washed with brine 30 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 to 0/1) to give methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,6-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 1.85 mmol, 64.46% yield, 97% purity) as a white solid. MS (ESI) m/z 523.1 $[M+H]^+$

[0001844] Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,6-dichloro-1H-indole-2-carboxamide

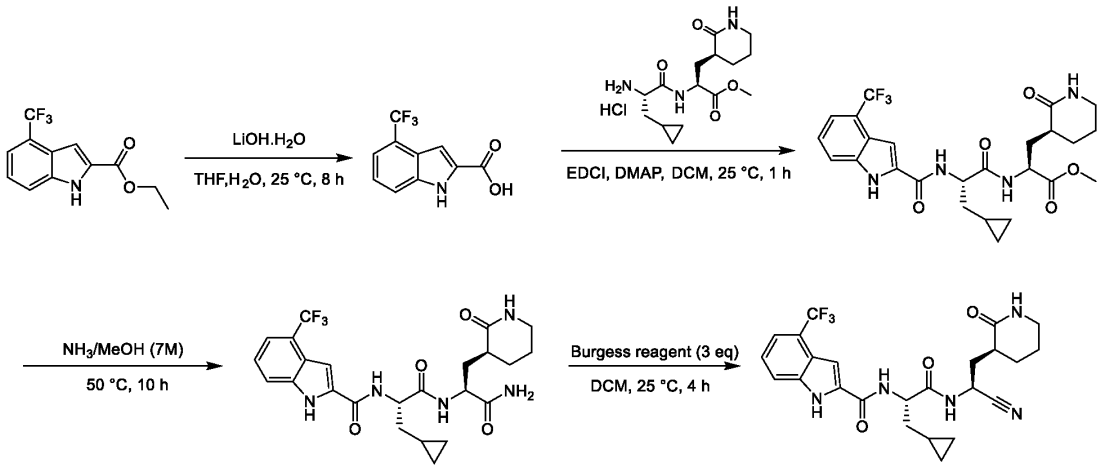
[0001845] To a solution of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,6-dichloro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (960 mg, 1.83 mmol, 1 eq) in NH_3/MeOH (7 M, 20 mL, 76.33 eq). The mixture was stirred at 50 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,6-dichloro-1H-indole-2-carboxamide (820 mg, crude) as a white solid. MS (ESI) m/z 508.1 $[M+H]^+$

[0001846] Step 3: 4,6-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001847] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,6-dichloro-1H-indole-2-carboxamide (800 mg, 1.57 mmol, 1 eq) in DCM (15 mL), then BURGESSREAGENT (749.98 mg, 3.15 mmol, 2 eq) was added. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150*50mm* 10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 40%-60%,10min), to give 4,6-dichloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (213.1 mg, 434.56 umol, 27.62% yield, 100% purity) as a white solid. MS (ESI) m/z 490.1 $[M+H]^+$

[0001848] ^1H NMR (400MHz, DMSO-d_6) δ = 12.11 (s, 1H), 8.95 (d, J = 8.4Hz, 1H), 8.84 (d, J = 7.4Hz, 1H), 7.53 (s, 1H), 7.44 (d, J = 17.4Hz, 2H), 7.24 (d, J = 1.8Hz, 1H), 5.13 - 5.01 (m, 1H), 4.52 - 4.41 (m, 1H), 3.19 - 3.00 (m, 2H), 2.35 - 2.18 (m, 2H), 1.97 - 1.63 (m, 4H), 1.61 - 1.33 (m, 3H), 0.88 - 0.75 (m, 1H), 0.51 - 0.32 (m, 2H), 0.25 - 0.05 (m, 2H)

Example 227. Synthesis of viral protease inhibitor compound 856



[0001849] Step 1: 4-(trifluoromethyl)-1H-indole-2-carboxylic acid

[0001850] To a solution of ethyl 4-(trifluoromethyl)-1H-indole-2-carboxylate (800 mg, 3.11 mmol, 1 eq) in THF (10 mL), H_2O (5 mL) was added $LiOH.H_2O$ (261.02 mg, 6.22 mmol, 2 eq) and the mixture was stirred at 25 °C for 8 h. The reaction mixture was adjust to pH~3 with HCl (1M, aq). The mixture was extracted with EtOAc (100 * 3 mL). The combined organiclayer was dried over Na_2SO_4, filtered, concentrated to give product 4-(trifluoromethyl)-1H-indole-2-carboxylic acid (700 mg, crude) was white solid. MS (ESI) m/z 230.0 $[M+H]^+$

[0001851] Step 2: (S)-methyl 2-((S)-3-cyclopropyl-2-(4-(trifluoromethyl)-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001852] To a solution of 4-(trifluoromethyl)-1H-indole-2-carboxylic acid (650 mg, 2.84 mmol, 1 eq) in DCM (20 mL) was added (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (986.64 mg, 2.84 mmol, 1 eq, HCl), DMAP (1.04 g, 8.51 mmol, 3 eq), EDCI (1.09 g, 5.67 mmol, 2 eq) and the mixture was stirred at 25 °C for 1 h. Upon completion, the reaction was quenched by addition H_2O (200 mL) and then extracted with EtOAc (100 mL * 3). The combined organic layers were washed with (brine 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by column chromatography (SiO_2, EtOAc/MeOH = 1/0 to 10/1) to give product (S)-methyl 2-((S)-3-cyclopropyl-2-(4-(trifluoromethyl)-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopiperidin-3-

yl)propanoate (800 mg, 1.50 mmol, 52.83% yield, 97.87% purity) as yellow solid. MS (ESI) m/z 523.2 $[M+H]^+$

[0001853] Step 3: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-(trifluoromethyl)-1H-indole-2-carboxamide

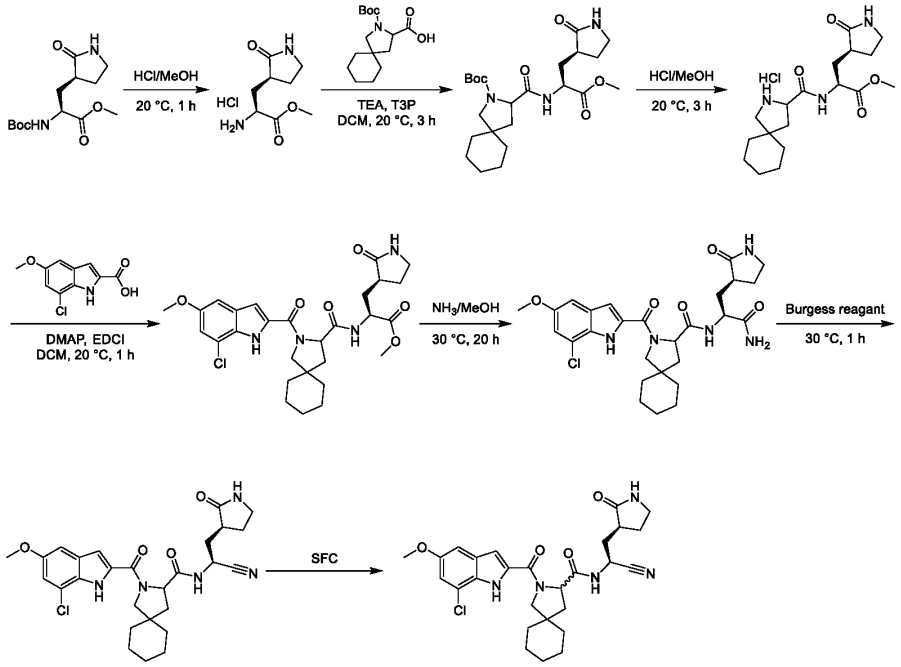
[0001854] To a solution of (S)-methyl 2-((S)-3-cyclopropyl-2-(4-(trifluoromethyl)-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (700 mg, 1.34 mmol, 1 eq) in ammonia (7 M, 40 mL, 209.01 eq) was stirred at 50 °C for 10 h. Upon completion, the reaction was concentrated in the vacuum to give crude product N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-(trifluoromethyl)-1H-indole-2-carboxamide (690 mg, crude) as white solid. MS (ESI) m/z 508.2 $[M+H]^+$

[0001855] Step 4: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-(trifluoromethyl)-1H-indole-2-carboxamide

[0001856] To a solution of N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-(trifluoromethyl)-1H-indole-2-carboxamide (670 mg, 1.32 mmol, 1 eq) in DCM (30 mL) was added BURGESS REAGENT (943.82 mg, 3.96 mmol, 3 eq) and the mixture was stirred at 25 °C for 4 h. Upon completion, the reaction was concentrated in the vacuum and was purified by prep-HPLC (column: Waters Xbridge C18 150 * 50mm * 10um; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min) to give prodcut N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-(trifluoromethyl)-1H-indole-2-carboxamide (200 mg, 408.59 umol, 30.95% yield, 100% purity) as white solid. MS (ESI) m/z 490.1 $[M+H]^+$

[0001857] ^1H NMR (400MHz, DMSO-d_6) δ = 12.14 (br s, 1H), 8.97 - 8.95 (m, 1H), 8.88 - 8.86 (m, 1H), 7.75 7.71 (m, 1H), 7.54 (s, 2H), 7.45 - 7.43 (m, 1H), 7.37 - 7.31 (m, 1H), 5.11 - 5.03 (m, 1H), 4.52 - 4.45 (m, 1H), 3.15 - 3.04 (m, 2H), 2.35 - 2.21 (m, 2H), 1.93 - 1.76 (m, 3H), 1.76 - 1.64 (m, 1H), 1.62 - 1.51 (m, 1H), 1.49 - 1.34 (m, 2H), 0.84 - 0.81 (m, 1H), 0.48 - 0.36 (m, 2H), 0.26 - 0.07 (m, 2H).

Example 228. Synthesis of viral protease inhibitor compound 896



[0001858] Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001859] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (2.6 g, 9.08 mmol, 1 *eq*) in HCl/MeOH (4 M, 30 mL, 13.21 *eq*) was stirred at 20 °C for 1.5 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (30 mL * 3) and concentrated under reduced pressure to get product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (2 g, crude, HCl) as yellow oil. MS (ESI) m/z 187.1 $[M+H]^+$.

[0001860] Step 2: tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate

[0001861] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (2 g, 8.98 mmol, 1 *eq*, HCl) in DCM (20 mL) and DMF (2 mL) then added 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (2.80 g, 9.88 mmol, 1.1 *eq*), T3P (11.43 g, 17.96 mmol, 10.68 mL, 50% purity, 2 *eq*) and TEA (5.45 g, 53.89 mmol, 7.50 mL, 6 *eq*) was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was

diluted with water (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 4/1~0/1) to get the product tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (2.5 g, 4.43 mmol, 49.31% yield, 80% purity) as white solid. MS (ESI) m/z 452.3 $[M+H]^+$.

[0001862] Step 3: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001863] A mixture of tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (2.1 g, 3.72 mmol, 80% purity, 1 *eq*) in HCl/MeOH (4 M, 25 mL, 26.88 *eq*) was stirred at 20 °C for 3 h. Upon completion, The mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to get the product methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.4 g, crude, HCl) as white oil. MS (ESI) m/z 352.2 $[M+H]^+$.

[0001864] Step 4: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[0001865] A mixture of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.4 g, 3.61 mmol, 1 *eq*, HCl) in DCM (20 mL) then added 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (1.06 g, 4.69 mmol, 1.3 *eq*), DMAP (1.10 g, 9.02 mmol, 2.5 *eq*) and EDCI (1.38 g, 7.22 mmol, 2 *eq*) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 2/1~0/1) to get the product methyl (2S)-2-[[2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.5 g, 2.68 mmol, 74.34% yield) as white solid. MS (ESI) m/z 559.2 $[M+H]^+$.

[0001866] Step 5: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001867] A mixture of methyl (2S)-2-[[2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.46 g, 2.61 mmol, 1 *eq*) in NH_3/MeOH (7 M, 20 mL, 53.61 *eq*) was stirred at 30 °C for 20 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (30 mL * 3) and concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.35 g, crude) as yellow oil. MS (ESI) m/z 544.2 $[M+H]^+$.

[0001868] Step 6: 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[0001869] A mixture of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.35 g, 2.11 mmol, 85% purity, 1 *eq*) in DCM (15 mL) added BURGESS REAGENT (1.51 g, 6.33 mmol, 3 *eq*) was stirred at 30 °C for 1 h. Upon completion, the mixture were quenched with water (1 mL) and blow-dried with N_2. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 35% - 65%, 8 min), which was further separated by SFC (column: REGIS(S,S)WHELK-O1 (250 mm * 25 mm, 10 um); mobile phase: [Neu-ETOH]; B%: 60% - 60%, 12 min) to get the product 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (322.82 mg, 613.70 umol, 29.10% yield) as white solid. MS (ESI) m/z 526.2 $[M+H]^+$.

[0001870] ^1H NMR (400 MHz, MeOD-d_4) δ = 7.12 (d, J=1.7 Hz, 1H), 7.02 (s, 1H), 6.97 (br d, J=1.8 Hz, 1H), 5.12 - 5.00 (m, 1H), 4.62 (dd, J=7.9, 9.7 Hz, 1H), 3.92 (br d, J=10.3 Hz, 1H), 3.86 - 3.33 (m, 5H), 3.30 - 3.26 (m, 1H), 2.77 - 2.55 (m, 1H), 2.52 - 2.23 (m, 3H), 1.98 - 1.67 (m, 3H), 1.62 - 1.41 (m, 10H).

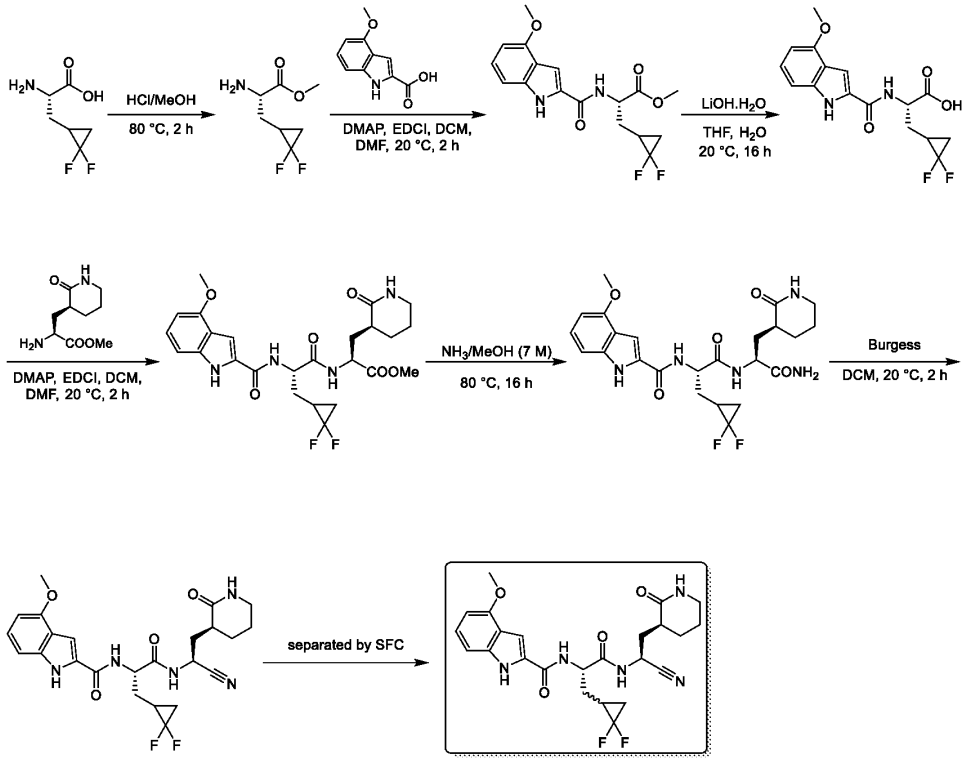
[0001871] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.07 (br d, J=1.1 Hz, 1H), 8.72 (br d, J=7.5 Hz, 1H), 7.44 (br d, J=0.7 Hz, 1H), 7.12 (br s, 1H), 6.97 (s, 2H), 4.92 (br s, 1H), 4.60 (br s, 1H), 3.85 - 3.77 (m, 4H), 3.61 (br s, 1H), 3.14 (br s, 2H), 2.43 - 2.21 (m, 2H), 2.20 - 1.89 (m, 2H), 1.80 (br s, 1H), 1.72 - 1.58 (m, 2H), 1.57 - 1.35 (m, 10H).

[0001872] To get the product 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (289.32 mg, 550.01 umol, 26.08% yield) as white solid. MS (ESI) m/z 526.2 $[M+H]^+$.

[0001873] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.12 (d, J=2.0 Hz, 1H), 7.04 (s, 1H), 6.99 - 6.93 (m, 1H), 5.06 - 4.97 (m, 1H), 4.63 (dd, J=7.9, 9.5 Hz, 1H), 3.94 (br d, J=10.4 Hz, 1H), 3.88 - 3.68 (m, 4H), 3.30 - 2.73 (m, 2H), 2.68 - 2.10 (m, 4H), 1.94 - 1.69 (m, 3H), 1.62 - 1.40 (m, 10H).

[0001874] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.46 - 10.49 (m, 1H), 8.67 (br d, J=6.6 Hz, 1H), 7.44 (br s, 1H), 7.21 - 7.07 (m, 1H), 6.98 (s, 2H), 5.06 - 4.83 (m, 1H), 4.59 (br dd, J=2.1, 4.1 Hz, 1H), 3.80 (s, 4H), 3.70 - 3.44 (m, 1H), 3.22 - 3.10 (m, 2H), 2.25 (s, 4H), 1.82 (br s, 1H), 1.68 (br d, J=10.4 Hz, 2H), 1.59 - 1.33 (m, 10H).

Example 229. Synthesis of viral protease inhibitor compound 1059



[0001875] Step 1: (2S)-2-amino-3-(2,2-difluorocyclopropyl)propanoic acid

[0001876] A mixture of (2S)-2-amino-3-(2,2-difluorocyclopropyl)propanoic acid (630 mg, 3.13 mmol, 1 eq, HCl) in HCl/MeOH (4 M, 6 mL, 7.68 eq) was stirred at 80 °C for 2 h. Upon completion, the mixture was concentrated under the reduced pressure to give methyl(2S)-2-amino-3-(2,2-difluorocyclopropyl)propanoate (700 mg, crude, HCl) as a yellow oil.

[0001877] Step 2: (2S)-methyl 3-(2,2-difluorocyclopropyl)-2-(4-methoxy-1H-indole-2-carboxamido)propanoate

[0001878] To a solution of methyl (2S)-2-amino-3-(2,2-difluorocyclopropyl)propanoate (700 mg, 3.25 mmol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (930.98 mg, 4.87 mmol, 1.5 eq) in DCM (15 mL) and DMF (3 mL) was added DMAP (793.21 mg, 6.49 mmol, 2 eq) and EDCI (1.24 g, 6.49 mmol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL), and then extracted with EA (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to

give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 10:1 to 0:1) to give methyl (2S)-3-(2,2-difluorocyclopropyl)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoate (1 g, 2.84 mmol, 87.43% yield) as a yellow oil. MS (ESI) m/z 353.1 $[M+H]^+$

[0001879] Step 3: (2S)-3-(2,2-difluorocyclopropyl)-2-(4-methoxy-1H-indole-2-carboxamido)propanoic acid

[0001880] To a solution of methyl (2S)-3-(2,2-difluorocyclopropyl)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoate (1 g, 2.84 mmol, 1 eq) in THF (10 mL) and H_2O (3 mL) was added $LiOH.H_2O$ (357.31 mg, 8.51 mmol, 3 eq). The mixture was stirred at 20 °C for 16 h. Upon completion, the mixture was quenched by addition H_2O (30 mL), and then added aq. HCl (1 M) to adjust the pH to 3-4, and extracted with EA (20 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (2S)-3-(2,2-difluorocyclopropyl)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (1 g, crude) as a yellow solid. MS (ESI) m/z 339.1 $[M+H]^+$

[0001881] Step 4: (2S)-methyl2-((2S)-3-(2,2-difluorocyclopropyl)-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001882] To a solution of (2S)-3-(2,2-difluorocyclopropyl)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (1 g, 2.96 mmol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (887.81 mg, 3.75 mmol, 1.27 eq, HCl) in DCM (15 mL) and DMF (3 mL) was added DMAP (722.23 mg, 5.91 mmol, 2 eq) and EDCI (1.13 g, 5.91 mmol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL), and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 10:1 to 0:1) to give methyl (2S)-2-[[(2S)-3-(2,2-difluorocyclopropyl)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 1.92 mmol, 64.99% yield) as a yellow solid. MS (ESI) m/z 521.2 $[M+H]^+$

[0001883] Step 5: N-((2S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001884] methyl(2S)-2-[[(2S)-3-(2,2-difluorocyclopropyl)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 1.92 mmol, 1 eq) in NH_3/MeOH (7 M, 15 mL, 54.66 eq) was stirred at 80 °C for 16 h. Upon completion, the mixture was concentrated under the reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (1 g, crude) as a brown solid. MS (ESI) m/z 506.2 $[M+H]^+$

[0001885] Step 6: N-((2S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001886] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (1 g, 1.98 mmol, 1 eq) in DCM (15 mL) was added BURGESS REAGENT (1.41 g, 5.93 mmol, 3 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150 * 50 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 25%-50%, 10 min) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxoethyl]-4-methoxy-1H-indole-2-carboxamide (0.6 g, 1.23 mmol, 62.22% yield) as a yellow solid. MS (ESI) m/z 488.2 $[M+H]^+$

[0001887] Step 7: N-((2S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[0001888] N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxoethyl]-4-methoxy-1H-indole-2-carboxamide (0.6 g, 1.23 mmol) was separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O IPA]; B%: 46% - 46%, 7 min) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-

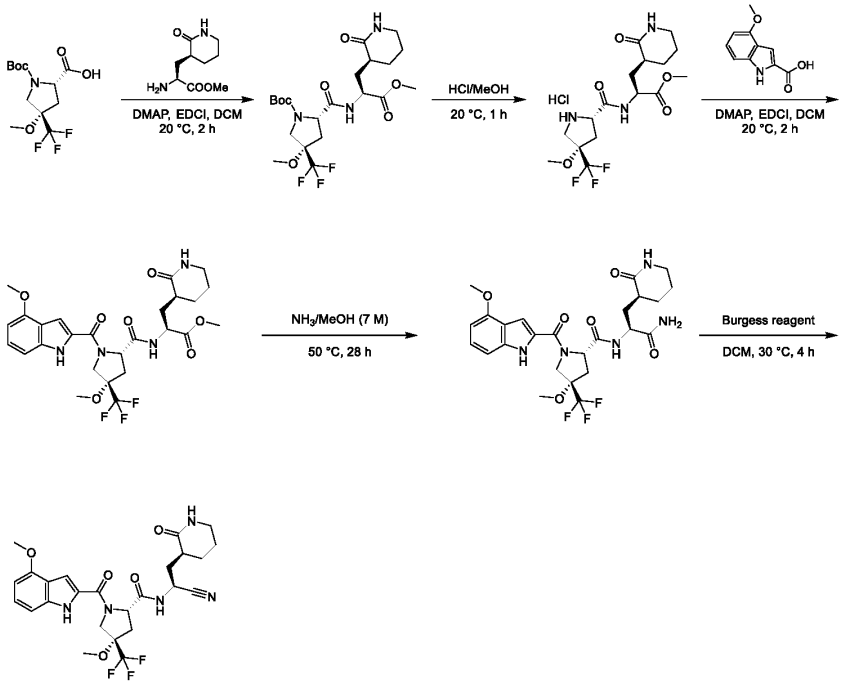
difluorocyclopropyl)methyl]-2-oxoethyl]-4-methoxy-1H-indole-2-carboxamide Isomer 1 (210 mg, 429.91 umol, 34.93% yield, 99.8% purity) as a white solid. MS (ESI) m/z 488.2 $[M+H]^+$

[0001889] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.27 - 7.26 (m, 1H), 7.17 - 7.15 (m, 1H), 7.13 - 7.04 (m, 1H), 6.52 – 6.50 (m, 1H), 5.14 – 5.09 (m, 1H), 4.61 – 4.56 (m, 1H), 3.93 (s, 3H), 3.23 – 3.21 (m, 2H), 2.46 - 2.42 (m, 2H), 1.96 – 1.95 (m, 1H), 1.93 – 1.92 (m, 3H), 1.85 - 1.70 (m, 3H), 1.56 - 1.44 (m, 2H), 1.22 - 1.12 (m, 1H)

[0001890] To give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxoethyl]-4-methoxy-1H-indole-2-carboxamide Isomer 2 (210 mg, 429.05 umol, 34.86% yield, 99.6% purity) as a white solid. MS (ESI) m/z 488.2 $[M+H]^+$

[0001891] 1H NMR (400 MHz, MeOD-d_4) δ = 7.32 - 7.24 (m, 1H), 7.20 - 7.11 (m, 1H), 7.13 - 7.05 (m, 1H), 6.53 – 6.51 (m, 1H), 5.14 - 5.00 (m, 1H), 4.66 – 4.61 (m, 1H), 3.94 (s, 3H), 3.20 – 3.19 (m, 2H), 2.43 - 2.25 (m, 2H), 1.95 – 1.90 (m, 4H), 1.85 - 1.63 (m, 3H), 1.56 - 1.44 (m, 2H), 1.22 - 1.03 (m, 1H)

Example 230. Synthesis of viral protease inhibitor compound 1155



[0001892] Step 1: tert-butyl (2S,4S)-4-methoxy-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate

[0001893] To a solution of (2S,4S)-1-tert-butoxycarbonyl-4-methoxy-4-(trifluoromethyl)pyrrolidine-2-carboxylic acid (0.5 g, 1.60 mmol, 1.2 eq), methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (314.82 mg, 1.33 mmol, 1 eq, HCl), EDCI (509.94 mg, 2.66 mmol, 2 eq) in DCM (5 mL) was added DMAP (487.48 mg, 3.99 mmol, 3 eq) and the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (100 mL) and extracted with DCM (15 mL * 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/1 to 0/1 and then DCM:MeOH = 5:1) to give product tert-butyl (2S,4S)-4-methoxy-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate (0.9 g, 1.27 mmol, 95.60% yield, 70% purity) as yellow oil. MS (ESI) m/z 496.2 $[M+H]^+$

[0001894] Step 2: methyl (2S)-2-[[(2S,4S)-4-methoxy-4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001895] To a solution of tert-butyl (2S,4S)-4-methoxy-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-4-(trifluoromethyl)pyrrolidine-1-carboxylate (0.8 g, 1.61 mmol, 1 eq) in HCl/MeOH (4 M, 9 mL, 22.30 eq) was stirred at 20 °C for 1 h. Upon completion, the reaction was concentrated under pressure reduced to give crude product methyl (2S)-2-[[(2S,4S)-4-methoxy-4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.65 g, crude, HCl) as yellow oil. MS (ESI) m/z 396.1 $[M+H]^+$

[0001896] Step 3: methyl (2S)-2-[[(2S,4S)-4-methoxy-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[0001897] To a solution of methyl (2S)-2-[[(2S,4S)-4-methoxy-4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.65 g, 1.51 mmol, 1 eq, HCl), 4-methoxy-1H-indole-2-carboxylic acid (345.32 mg, 1.81 mmol, 1.2 eq) in DCM (5 mL) was added DMAP (551.67 mg, 4.52 mmol, 3 eq) and EDCI (577.10 mg, 3.01 mmol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction was quenched by addition H_2O (80 mL) and extracted with DCM (10 mL * 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/1 to 0/1) to give the product methyl (2S)-2-[[(2S,4S)-4-methoxy-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.65 g, crude) as yellow oil. MS (ESI) m/z 569.2 $[M+H]^+$

[0001898] Step 4: (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-4-methoxy-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide

[0001899] To a solution of methyl (2S)-2-[[(2S,4S)-4-methoxy-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.53 g, 932.21 umol, 1 eq) in NH_3/MeOH (3 mL) was stirred at 50 °C for 28 h. Upon completion, the reaction was concentrated under pressure reduced to get the crude product (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-

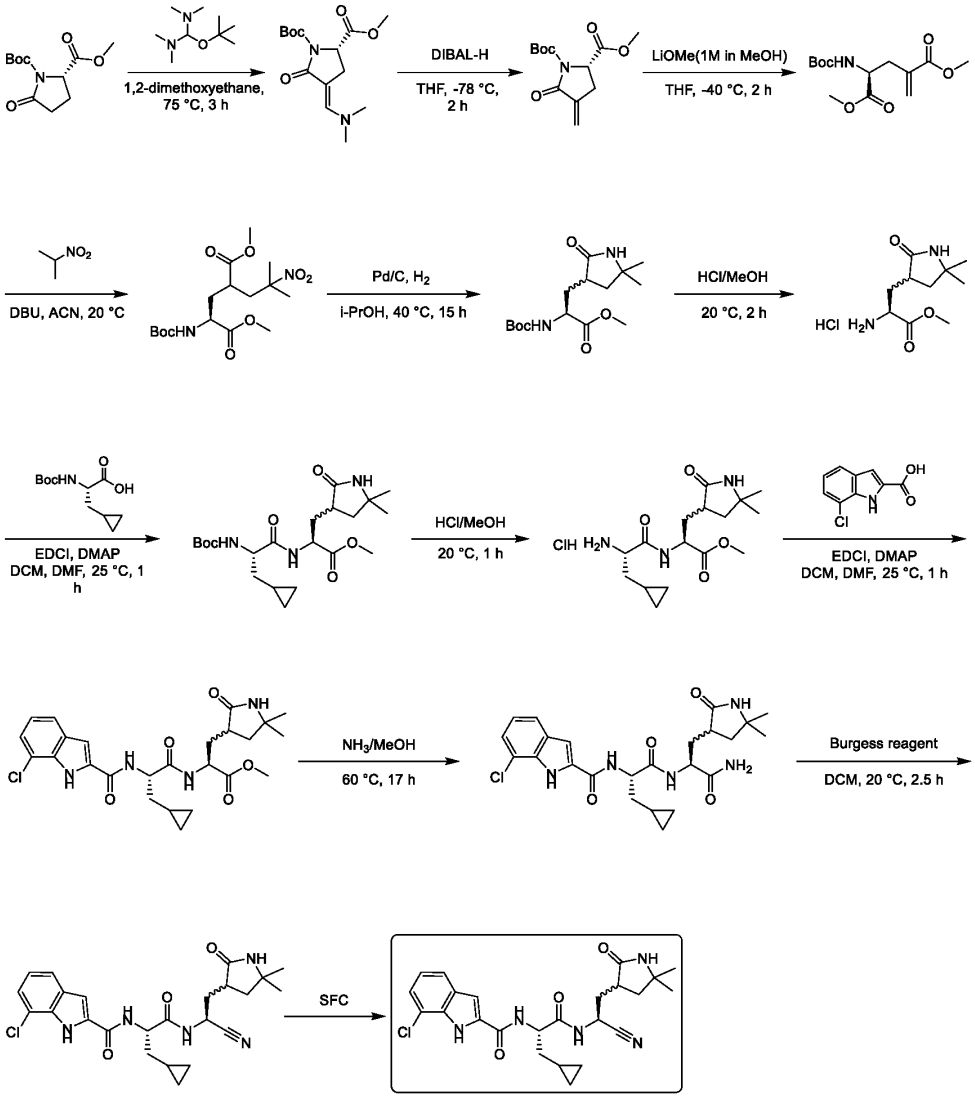
piperidyl]methyl]ethyl]-4-methoxy-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide (0.5 g, crude) as yellow solid. MS (ESI) m/z 554.2 $[M+H]^+$

[0001900] Step 5: (2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-4-methoxy-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide

[0001901] To a solution of (2S,4S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-4-methoxy-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide (0.5 g, 812.96 umol, 90% purity, 1 eq) in DCM (8 mL) was added BURGESS REAGENT (581.21 mg, 2.44 mmol, 3 eq) and the mixture was stirred at 30 °C for 4 h. Upon completion, the mixture were quenched with water(1.5 mL) and blow-dried with N_2 and was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-50%,8min) to give product (2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-4-methoxy-1-(4-methoxy-1H-indole-2-carbonyl)-4-(trifluoromethyl)pyrrolidine-2-carboxamide (0.21 g, 392.15 umol, 48.24% yield, 100% purity) as white solid. MS (ESI) m/z 536.2 $[M+H]^+$

[0001902] ^1H NMR (400MHz, DMSO-d_6) δ = 7.25 - 7.13 (m, 1H), 7.05 (br d, J = 8.2 Hz, 2H), 6.63 - 6.40 (m, 1H), 5.36 - 4.89 (m, 2H), 4.47 - 4.04 (m, 2H), 4.02 - 3.79 (m, 3H), 3.45 (br s, 3H), 3.26 - 2.90 (m, 2H), 2.86 - 2.50 (m, 2H), 2.49 - 2.14 (m, 2H), 2.04 - 1.04 (m, 5H).

Example 231. Synthesis of viral protease inhibitor compound 1053



[0001903] Step 1: O1-tert-butylO2-methyl(2S,4E)-4-(dimethylaminomethylene)-5-oxo-pyrrolidine-1,2-dicarboxylae

[0001904] A mixture of O1-tert-butyl O2-methyl (2S)-5-oxopyrrolidine-1,2-dicarboxylate (282 g, 1.16 mol, 1 eq), 1-tert-butoxy-N,N,N',N'-tetramethyl-methanediamine (303.06 g, 1.74 mol, 359.08 mL, 1.5 eq) in DME (282 mL) was stirred at 75 °C for 3 h. Upon completion, the mixture was cooled to 0 °C and then filtered, the filter cake was concentrated under the reduced pressure to give the product O1-tert-butylO2-methyl(2S,4E)-4-(dimethylaminomethylene)-5-oxo-pyrrolidine-1,2-dicarboxylae(272 g, crude) as a white solid.

[0001905] Step 2: O1-tert-butyl O2-methyl (2S)-4-methylene-5-oxo-pyrrolidine-1,2-dicarboxylate

[0001906] To a solution of O1-tert-butyl O2-methyl (2S,4E)-4-(dimethylaminomethylene)-5-oxo-pyrrolidine-1,2-dicarboxylate (70 g, 234.64 mmol, 1 eq) in THF (700 mL) was added DIBAL-H (1 M, 703.91 mL, 3 eq) at -78 °C. The mixture was stirred at -78 °C for 2 h. Upon completion, the reaction mixture was quenched by added to sat. NH_4Cl (2500 mL) and then extracted with EA (1000 mL * 3). The combined organic layers were washed with brine (2000 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give the product. The product O1-tert-butyl O2-methyl (2S)-4-methylene-5-oxo-pyrrolidine- 1,2-dicarboxylate (35 g, 137.11 mmol, 58.44% yield) was obtained as a white solid.

[0001907] Step 3: dimethyl (2S)-2-(tert-butoxycarbonylamino)-4-methylene-pentanedioate

[0001908] To a solution of O1-tert-butyl O2-methyl (2S)-4-methylene-5-oxo-pyrrolidine-1,2-dicarboxylate (25 g, 97.94 mmol, 1 eq) in THF (250 mL) was added lithium;methanolate (1 M, 117.52 mL, 1.2 eq) at -40 °C. The solution was stirred for 2 h at -40 °C. Upon completion, the solution was quenched with NH_4Cl (70 mL) and concentrated and extracted with EA (80 mL * 2) and concentrated to give crude dimethyl (2S)-2-(tert-butoxycarbonylamino)-4-methylene-pentanedioate (24 g, crude) as a yellow oil and used directly for the next step. MS (ESI) m/z 188.1 $[M+H-100]^+$

[0001909] Step 4: dimethyl (2S)-2-(tert-butoxycarbonylamino)-4-(2-methyl-2-nitro-propyl)pentanedioate

[0001910] To a solution of dimethyl (2S)-2-(tert-butoxycarbonylamino)-4-methylene-pentanedioate (34 g, 118.34 mmol, 1 eq) and 2-nitropropane (11.60 g, 130.17 mmol, 11.69 mL, 1.1 eq) in ACN (350 mL) was added DBU (21.62 g, 142.01 mmol, 21.40 mL, 1.2 eq). The solution was stirred for 2 h at 20 °C. Upon completion, the solution was concentrated to give crude. The crude was purified by column (SiO_2, PE:EA = 20:1 to 1:1) to give product compound dimethyl (2S)-2-(tert-butoxycarbonylamino)-4-(2-

methyl-2-nitro-propyl)pentanedioate (30 g, 79.70 mmol, 67.35% yield) as a white solid. MS (ESI) m/z 277.1 $[M+H-100]^+$

[0001911] Step 5: methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate

[0001912] To a solution of dimethyl (2S)-2-(tert-butoxycarbonylamino)-4-(2-methyl-2-nitro-propyl)pen tanedioate (26 g, 69.08 mmol, 1 eq) in IPA (250 mL) was added Pd/C (24.54 g, 20.72 mmol, 10% purity, 0.3 eq) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 40 °C for 15 h. Upon completion, the mixture was filtered and concentrated to give crude compound. The crude was purified by column(SiO_2, PE:EA = 20:1 to 0:1) to give product methyl (2S)-2-(tert-butoxycarbony lamino)-3-(5,5-dimethyl -2-oxo-pyrrolidin-3-yl)propanoate (14.6 g, 46.44mmol, 67.23%) as a white solid and continue purified by SFC (column: DAICEL CHIRALPAK IC(250mm*50mm,10um);mobile phase: [0.1%NH_3H_2O IPA];B%: 30%-30%,11.5min) to give BB7 methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (4.8 g, 15.27 mmol, 32.65% yield) as a white solid. MS (ESI) m/z 315.2 $[M+H]^+$

[0001913] Step 6: methyl (2S)-2-amino-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate

[0001914] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl) propanoate (500 mg, 1.59 mmol, 1 eq) in HCl/MeOH (10 mL) was stirred at 20 °C for 2 h. Upon completion, the solution was concentrated to dryness to give crude compound methyl (2S)-2-amino-3- (5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (398 mg, crude, HCl) as a white solid and used directly for the next step.

[0001915] Step 7: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(5,5- dimethyl-2-oxo-pyrrolidin-3-yl)propanoate

[0001916] To a solution of methyl (2S)-2-amino-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (370 mg, 1.48 mmol, 1 eq, HCl) in DCM (10 mL) and DMF (5 mL) was added DMAP (360.58 mg, 2.95 mmol, 2 eq) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (372.18 mg, 1.62 mmol, 1.1 eq) and EDCI (565.80 mg, 2.95 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was

diluted with H_2O (60 mL) and extracted with EA (60 mL * 3) and concentrated to give crude. The crude was purified by column (SiO_2, PE:EA = 10:1 to 0:1) to give compound methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl] amino]-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (550 mg, 1.29 mmol, 87.59% yield) as a yellow oil. MS (ESI) m/z 426.2 $[M+H]^+$

[0001917] Step 8: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5,5-dimethyl-2-oxo- pyrrolidin -3-yl)propanoate

[0001918] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino] -3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (540 mg, 1.27 mmol, 1 eq) in HCl/MeOH (15 mL) was stirred at 20 °C for 1 h. Upon completion, the solution was concentrated to dryness to give crude compound methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5,5-dimethyl-2- oxo-pyrrolidin-3-yl)propanoate (456 mg, crude, HCl) as a white solid.

[0001919] Step 9: methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino] -3-cyclopropyl-propanoyl] amino]-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate

[0001920] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5,5-dimethyl -2-oxo-pyrrolidin-3-yl)propanoate (450 mg, 1.24 mmol, 1 eq, HCl) in DCM (10 mL) and DMF (5 mL) was added DMAP (303.85 mg, 2.49 mmol, 2 eq) and 7-chloro-1H-indole-2-carboxylic acid (243.24 mg, 1.24 mmol, 1 eq) and EDCI (476.79 mg, 2.49 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the solution was diluted with H_2O (60 mL) and extracted with EA (70 mL * 3) and washed with brine (100 mL * 2) and concentrated to give crude. The crude was purified by column (SiO_2, PE:EA = 3:1 to 0:1) to give product methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl) amino]-3-cyclopropyl-propanoyl]amino]-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (550 mg, 1.09 mmol, 87.93% yield) as a white solid. MS (ESI) m/z 503.2 $[M+H]^+$

[0001921] Step 10: N-[(1S)-2-[[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo-ethyl]amino] -1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide

[0001922] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl- propanoyl]amino]-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (550 mg, 1.09 mmol, 1 eq) in NH_3/MeOH (7 M, 7.81 mL, 50 eq) was stirred at 60 °C for 17 h. Upon completion, the solution was concentrated to dryness to give crude. The crude was used directly for the next step. Compound N-[(1S)-2-[[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (530 mg, crude) was obtained as a white solid. MS (ESI) m/z 488.2 $[M+H]^+$

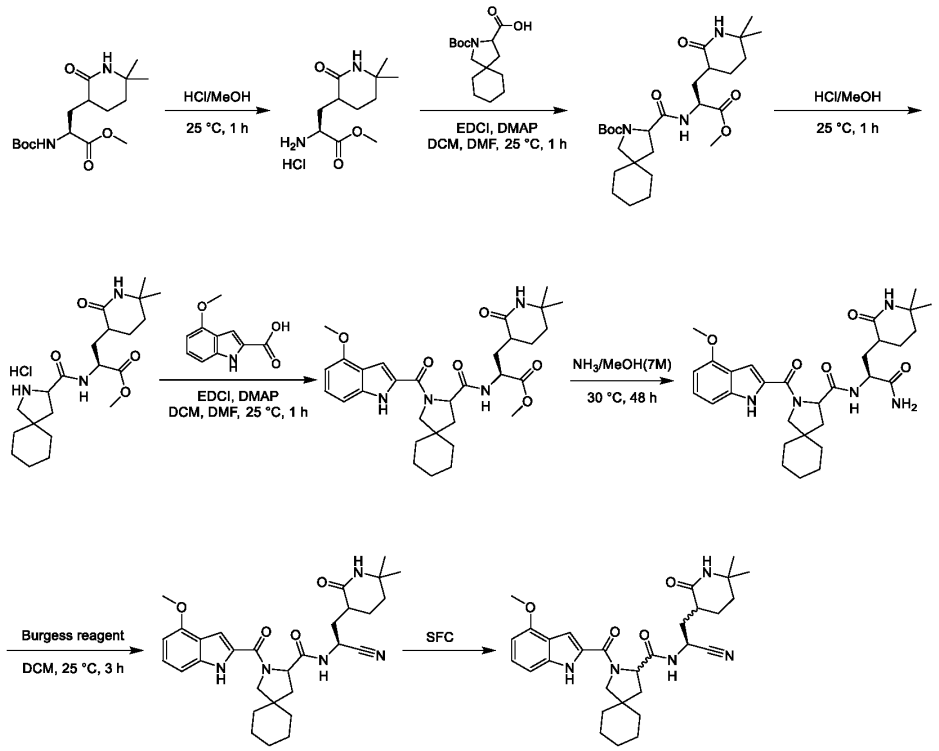
[0001923] Step 11: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]amino] -1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[0001924] To a solution of N-[(1S)-2-[[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo- ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (530 mg, 1.09 mmol, 1 eq) in DCM (20 mL) was added BURGESS REAGENT (517.65 mg, 2.17 mmol, 2 eq). The mixture was stirred at 20 °C for 2.5 h. Upon the reaction was completion, the solution was washed with H_2O (30 mL) and the organic phase was blowed dry with N_2 to give crude. The crude was purified by neutral pre-HPLC (Waters Xbridge C18 150 * 50mm * 10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-70%,10min) to give product. MS (ESI) m/z 470.2 $[M+H]^+$

[0001925] 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]amino] -1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (330 mg, 702.18 umol, 64.65% yield) was obtained as a white solid.

[0001926] ^1H NMR (400MHz, DMSO-d_6) Shift = 11.56 (br s, 1H), 8.89 (d, J=7.9 Hz, 1H), 8.60 (d, J=7.5 Hz, 1H), 7.70 (s, 1H), 7.50 (d, J=7.9 Hz, 1H), 7.19 (d, J=7.6 Hz, 1H), 7.12 (s, 1H), 6.95 (t, J=7.8 Hz, 1H), 4.95 - 4.76 (m, 1H), 4.46 - 4.20 (m, 1H), 2.52 - 2.44 (m, 1H), 2.12 - 1.99 (m, 1H), 1.88 (dd, J=8.6, 12.2 Hz, 1H), 1.76 - 1.60 (m, 2H), 1.45 - 1.33 (m, 2H), 1.03 (s, 3H), 0.95 (s, 3H), 0.76 - 0.62 (m, 1H), 0.38 - 0.25 (m, 2H), 0.14 - -0.06 (m, 2H).

Example 232. Synthesis of viral protease inhibitor compound 1111



[0001927] Step 1: methyl (2S)-2-amino-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate

[0001928] methyl (2S)-2-(tert-butoxycarbonylamino)-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (20 mg, 60.90 umol, 1 eq) was added HCl/MeOH (4 M, 5 mL, 328.40 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was used next step directly. Compound methyl (2S)-2-amino-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (16 mg, 57.41 umol, 94.27% yield, 95% purity, HCl) was obtained as a colourless oil.

[0001929] Step 2: tert-butyl 3-[[(1S)-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-methoxy-2-oxo-ethyl] carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate

[0001930] To a mixture of 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (171.25 mg, 604.35 umol, 1 eq) and methyl (2S)-2-amino-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (160 mg, 604.35 umol, 1 eq, HCl) in DMF (3 mL) and DCM (6 mL) was added EDCI (231.71 mg, 1.21 mmol, 2 eq) and DMAP (147.67 mg, 1.21 mmol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was

diluted with H_2O 20 mL and extracted with DCM 50 mL (25 mL * 2). The combined organic layers were washed with BRINE 20 mL (20 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=7/1 to 1/1) to get the compound tert-butyl 3-[[(1S)-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (195 mg, 395.03 umol, 65.36% yield, N/A purity) as a colourless oil.

[0001931] Step 3: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-(6,6-dimethyl-2-oxo-3-piperidyl) propanoate

[0001932] tert-butyl 3-[[(1S)-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-methoxy-2-oxo-ethyl]carbamoyl] -2-azaspiro[4.5]decane-2-carboxylate (170 mg, 344.38 umol, 1 eq) was added HCl/MeOH (4 M, 17.00 mL, 197.45 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was used next step directly. Compound methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-(6,6-dimethyl-2-oxo-3- piperidyl)propanoate (145 mg, 320.36 umol, 93.03% yield, 95% purity, HCl) was obtained as a colourless oil.

[0001933] Step 4: methyl (2S)-3-(6,6-dimethyl-2-oxo-3-piperidyl)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2- azaspiro[4.5]decane-3-carbonyl]amino]propanoate

[0001934] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (64.47 mg, 337.23 umol, 1 eq) and methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-(6,6-dimethyl-2-oxo-3-piperidyl)propanoate (145 mg, 337.23 umol, 1 eq, HCl) in DCM (6 mL) and DMF (3 mL) was added DMAP (82.40 mg, 674.45 umol, 2 eq) and EDCI (129.29 mg, 674.45 umol, 2 eq). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O 30 mL and extracted with EA 100 mL (50 mL * 2). The combined organic layers were washed with BRINE 50 mL (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (DCM: MeOH = 10: 1) to get the compound methyl (2S)-3-(6,6-dimethyl-2-oxo-3-piperidyl)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]propanoate (200 mg, 335.28 umol, 99.42% yield, 95% purity) as a yellow oil. MS (ESI) m/z 567.3 $[M+H]^+$

[0001935] Step 5: N-[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-oxo-ethyl]-2-(4-methoxy-1H-indole-2 -carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[0001936] To a mixture of methyl (2S)-3-(6,6-dimethyl-2-oxo-3-piperidyl)-2-[[2-(4-methoxy-1H-indole- 2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]propanoate (200 mg, 352.93 umol, 1 eq) was added NH_3/MeOH (7 M, 50.42 uL, 1 eq). The mixture was stirred at 30 °C for 48 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue and the residue was used next step directly. Compound N-[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl) methyl]-2-oxo-ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (190 mg, 309.96 umol, 87.83% yield, 90% purity) was obtained as a white solid. MS (ESI) m/z 552.3 $[M+H]^+$

[0001937] Step 6: N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-(4-methoxy-1H-indole-2-carbonyl) -2-azaspiro[4.5]decane-3-carboxamide

[0001938] To a mixture of N-[(1S)-2-amino-1-[(6,6-dimethyl-2-oxo-3-piperidyl)methyl]-2-oxo-ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (190 mg, 344.41 umol, 1 eq) in DCM (2 mL) was added BURGESS REAGENT (164.15 mg, 688.81 umol, 2 eq). The mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was diluted with H_2O 5 mL and extracted with DCM 10 mL (5 mL * 2). The combined organic layers were concentrated by blow-drying to give a residue. The residue was purified by prep-HPLC (neutral condition) (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water (10mM NH4HCO3)-ACN]; B%: 30%-60%, 10 min) to give desired compound (80 mg) as a white solid. The white solid was spereted by SFC (column: REGIS(S, S)WHELK-O1(250mm*25mm,10um);mobile phase: [Neu-ETOH];B%: 60%-60%,7min) to get the Isomers 1, 2, 3 & 4. The mixture (Isomers 2 &3) was separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [Neu-MeOH];B%: 50%-50%,15min). MS (ESI) m/z 534.2 $[M+H]^+$

[0001939] Isomer 1: Compound N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-(4-methoxy-1H-indole-2- carbonyl)-2-azaspiro[4.5]decane-3-

carboxamide (13 mg, 24.36 umol, 7.07% yield, 100% purity) was obtained as a white solid.

[0001940] ^{1}H NMR (400MHz, DMSO-d6) δ = 11.29 (br s, 1H), 8.69 (br s, 1H), 7.28 - 6.72 (m, 4H), 6.52 (d, J=7.7 Hz, 1H), 4.99 (br s, 1H), 4.78 - 4.46 (m, 1H), 3.95 - 3.82 (m, 4H), 3.73 - 3.40 (m, 1H), 2.34 - 2.04 (m, 3H), 1.89 - 1.31 (m, 16H), 1.13 (br d, J=10.6 Hz, 6H)

[0001941] Isomer 2: Compound N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-(4-methoxy-1H-indole-2- carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (17 mg, 31.86 umol, 9.25% yield, 100% purity) was obtained as a white solid.

[0001942] ^{1}H NMR (400MHz, DMSO-d6) δ = 11.31 (br s, 1H), 8.64 (br s, 1H), 7.25 - 6.75 (m, 4H), 6.52 (d, J=7.7 Hz, 1H), 4.99 (q, J=8.0 Hz, 1H), 4.61 (br s, 1H), 4.01 - 3.80 (m, 4H), 3.66 (br s, 1H), 2.30 - 1.94 (m, 3H), 1.92 - 1.31 (m, 16H), 1.12 (d, J=6.4 Hz, 6H)

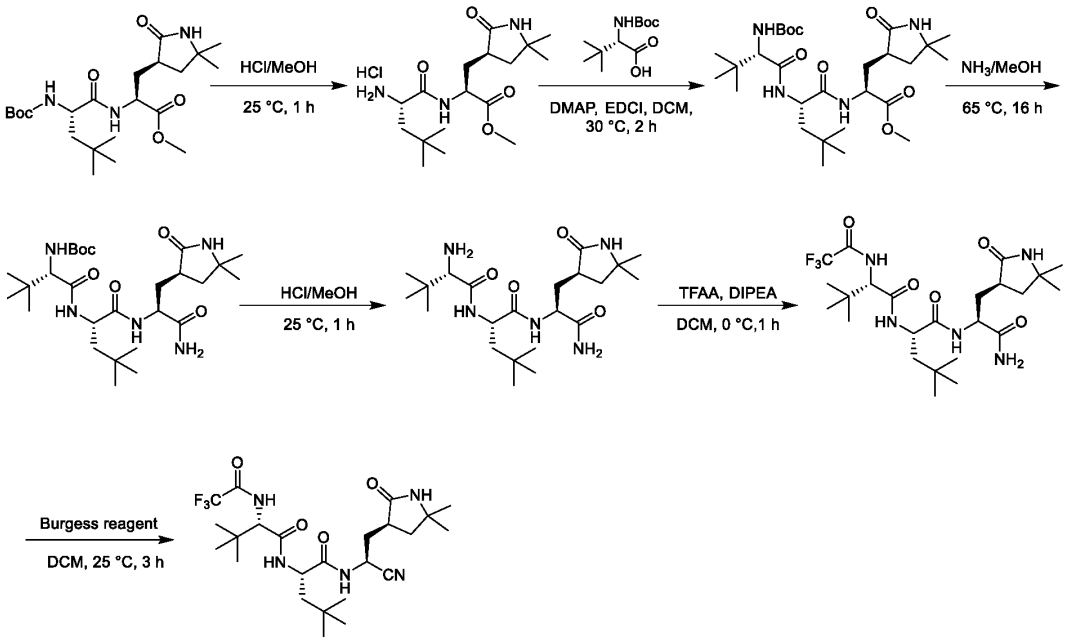
[0001943] Isomer 3: Compound N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-(4-methoxy-1H-indole-2- carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (14 mg, 26.23 umol, 7.62% yield, 100% purity) was obtained as a white solid.

[0001944] ^{1}H NMR (400MHz, DMSO-d6) δ = 11.30 (br s, 1H), 8.92 - 8.52 (m, 1H), 7.41 - 6.74 (m, 4H), 6.52 (br d, J=7.3 Hz, 1H), 4.94 (br s, 1H), 4.63 (br s, 1H), 4.03 - 3.78 (m, 4H), 3.73 - 3.44 (m, 1H), 2.35 - 2.04 (m, 3H), 1.93 - 1.32 (m, 16H), 1.14 (s, 6H)

[0001945] Isomer 4: Compound N-[(1S)-1-cyano-2-(6,6-dimethyl-2-oxo-3-piperidyl)ethyl]-2-(4-methoxy-1H-indole-2- carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (28 mg, 52.23 umol, 15.16% yield, 99.538% purity) was obtained as a white solid.

[0001946] ^{1}H NMR (400MHz, DMSO-d6) δ = 11.31 (br s, 1H), 8.69 (br s, 1H), 7.27 - 6.77 (m, 4H), 6.53 (d, J=7.5 Hz, 1H), 4.94 (br s, 1H), 4.61 (br s, 1H), 4.06 - 3.83 (m, 4H), 3.66 (br s, 1H), 2.32 - 1.98 (m, 3H), 1.83 - 1.32 (m, 16H), 1.13 (d, J=18.1 Hz, 6H)

Example 233. Synthesis of viral protease inhibitor compound 3069



[0001947] Step 1: (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[0001948] A solution of (S)-methyl 2-((S)-2-((tert-butoxycarbonyl) amino)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (400 mg, 905.88 umol, 1 eq) in HCl/MeOH (5 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (330 mg, crude, HCl) as a white solid. MS (ESI) m/z 342.2 $[M+H]^+$.

[0001949] Step 2: (6S,9S,12S)-methyl 6-(tert-butyl)-12-(((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyl-9-neopentyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate

[0001950] To a solution of (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (330 mg, 873.23 umol, 1 eq, HCl) and (S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (201.97 mg, 873.23 umol, 1 eq) in DCM (10 mL), was added DMAP (320.05 mg, 2.62 mmol, 3 eq) and EDCI (502.20 mg, 2.62 mmol, 3 eq). The mixture was stirred at 30 °C for 2 h. Upon completion, the

reaction mixture was quenched by addition H_2O (10 mL), and then extracted with DCM (5 mL * 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (6S,9S, 12S)-methyl 6-(tert-butyl)-12-(((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyl-9-neopentyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (450 mg, crude) as a white solid. MS (ESI) m/z 555.4 $[M+H]^+$.

[0001951] Step 3: tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate

[0001952] A solution of (6S,9S,12S)-methyl 6-(tert-butyl)-12-(((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyl-9-neopentyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (400 mg, 721.09 umol, 1 eq) in NH_3/MeOH (7 M, 8.00 mL, 77.66 eq) was stirred at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (430 mg, crude) as a white solid. MS (ESI) m/z 540.4 $[M+H]^+$.

[0001953] Step 4: (S)-2-((S)-2-amino-3,3-dimethylbutanamido)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-4,4-dimethylpentanamide

[0001954] A solution of tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (410 mg, 759.67 umol, 1 eq) in HCl/EtOAc (4 M, 189.92 uL, 1 eq) was stirred at 25 °C for 1 h. Upon completion, the resulting solution was concentrated in vacuum (40 °C) to give (S)-2-((S)-2-amino-3,3-dimethylbutanamido)-N-((S)-1-amino-3-((R)-5, 5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-4, 4-dimethylpentanamide (340 mg, crude) as a white solid. MS (ESI) m/z 440.3 $[M+H]^+$

[0001955] Step 5: (S)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide

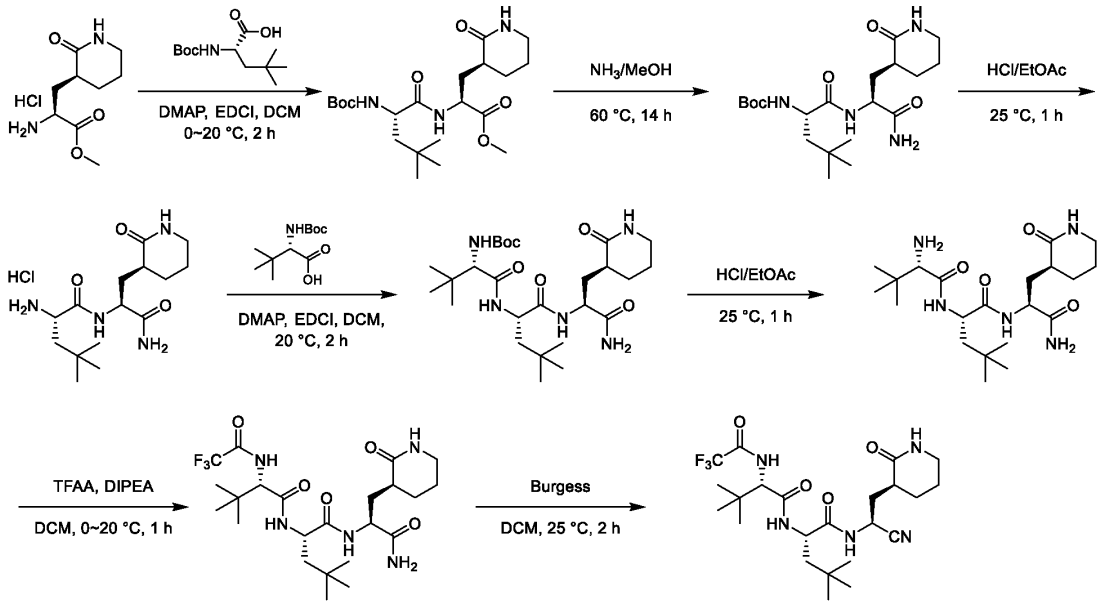
[0001956] To a solution of (S)-2-((S)-2-amino-3,3-dimethylbutanamido)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-4,4-dimethylpentanamide (300 mg, 682.45 umol, 1 eq) in DCM (3 mL) was added TFAA (86.00 mg, 409.47 umol, 56.95 uL, 0.6 eq) and DIPEA (264.61 mg, 2.05 mmol, 356.61 uL, 3 eq), the mixture was stirred at 0 °C for 1 h. LCMS showed most starting material was remained and then was added TFAA (28.67 mg, 136.49 umol, 18.98 uL, 0.2 eq) and the mixture was stirred for another 1 h. LCMS showed a little starting material was remained and then TFAA (43.00 mg, 204.74 umol, 28.48 uL, 0.3 eq) was added and was stirred for another 30 min. Upon completion, the resulting solution was poured into H_2O (10 mL), adjusted to pH~8 with $NaHCO_3$ and then extracted with EtOAc (10 mL * 2). The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give the crude product (S)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide (290 mg, crude) as a white solid. MS (ESI) m/z 536.3 $[M+H]^+$

[0001957] Step 6: (S)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide

[0001958] To a solution of (S)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide (290 mg, 541.45 umol, 1 eq) in DCM (3 mL) was added BURGESS REAGENT (258.06 mg, 1.08 mmol, 2 eq) then the mixture was stirred at 25 °C for 3 h. Upon completion, the resulting solution was quenched with H_2O (0.3 mL), then was concentrated in vacuum (25 °C). The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 * 30 mm * 3 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 30%-60%, 8 min) to give (S)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide (75.94 mg, 146.72 umol, 27.10% yield, 100% purity) as a white solid. MS (ESI) m/z 518.3 $[M+H]^+$.

[0001959] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 4.96 - 4.91 (m, 1H), 4.46 - 4.37 (m, 2H), 2.78 - 2.64 (m, 1H), 2.37 - 2.27 (m, 1H), 2.22 - 2.14 (m, 1H), 1.95 - 1.84 (m, 1H), 1.74 - 1.59 (m, 3H), 1.29 (s, 3H), 1.23 (s, 3H), 1.00 - 0.96 (m, 18H)

Example 234. Synthesis of viral protease inhibitor compound 3129



[0001960] Step 1: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001961] A mixture of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 3.80 mmol, 90% purity, 1 *eq*, HCl) and (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (1.03 g, 4.18 mmol, 1.1 *eq*) in DCM (10 mL) was added DMAP (1.16 g, 9.51 mmol, 2.5 *eq*), EDCI (1.46 g, 7.60 mmol, 2 *eq*) at 0 °C, then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (5 mL), and then diluted with H_2O (10 mL) and extracted with DCM 60 mL (30 mL * 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 0:1 to 10:1) to give (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-

3-yl)propanoate (1.14 g, 2.32 mmol, 61.01% yield, 87% purity) as yellow solid. MS (ESI) *m/z* 428.2 $[M+H]^+$.

[0001962] Step 2: tert-butyl ((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate

[0001963] A solution of (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1 g, 2.03 mmol, 87% purity, 1 *eq*) in NH_3/MeOH (7 M, 15 mL, 51.60 *eq*) was stirred at 60 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give tert-butyl ((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate (1 g, crude) as a yellow solid. MS (ESI) *m/z* 413.2 $[M+H]^+$.

[0001964] Step 3: (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide

[0001965] A solution of tert-butyl ((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate (1 g, 2.01 mmol, 83% purity, 1 eq) in HCl/EtOAc (4 M, 8.30 mL, 16.50 eq) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide (800 mg, crude) as a yellow solid. MS (ESI) *m/z* 313.2 $[M+H]^+$.

[0001966] Step 4: tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate

[0001967] To a mixture of (S)-2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide (700 mg, 1.57 mmol, 78% purity, 1 *eq*, HCl) and (2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoic acid (433.33 mg, 1.87 mmol, 1.2 *eq*) in DCM (10 mL) was added DMAP (478.01 mg, 3.91 mmol, 2.5 *eq*), EDCI (600.05 mg, 3.13 mmol, 2 *eq*) at 0 °C, then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with 1 N HCl (10 mL), then

washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 0:1 to 10:1) to give tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (400 mg, 684.83 umol, 43.76% yield, 90% purity) as yellow solid. MS (ESI) *m/z* 526.4 $[M+H]^+$.

[0001968] Step 5: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-((S)-2-amino-3,3-dimethylbutanamido)-4,4-dimethylpentanamide

[0001969] A mixture of tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (300 mg, 513.62 umol, 90% purity, 1 *eq*) in HCl/EtOAc (4 M, 2.70 mL, 21.03 *eq*) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-((S)-2-amino-3,3-dimethylbutanamido)-4,4-dimethylpentanamide (240 mg, crude, HCl) as yellow solid. MS (ESI) *m/z* 426.4 $[M+H]^+$.

[0001970] Step 6: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide

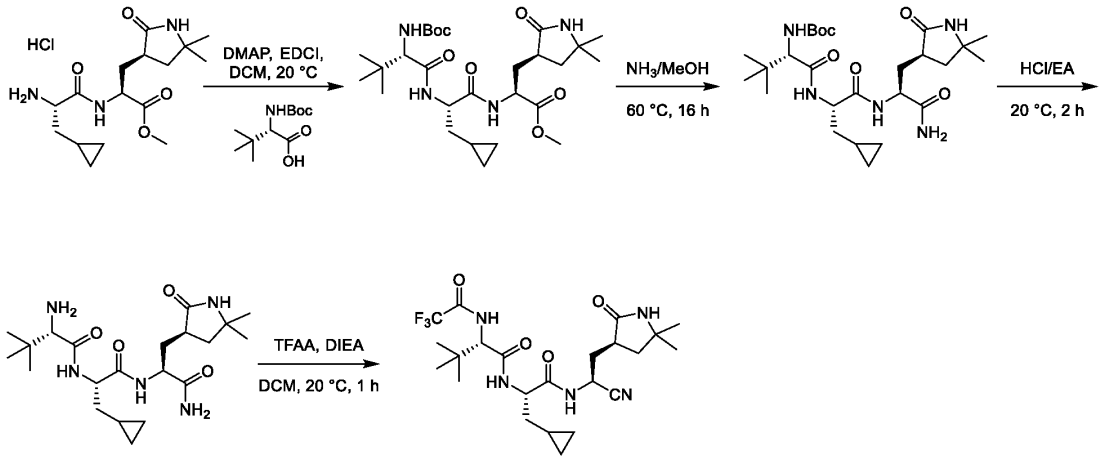
[0001971] To a mixture of (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-((S)-2-amino-3,3-dimethylbutanamido)-4,4-dimethylpentanamide (280 mg, 484.82 umol, 80% purity, 1 eq, HCl) in DCM (3 mL) was added DIEA (187.98 mg, 1.45 mmol, 253.34 uL, 3 eq) and TFAA (152.74 mg, 727.23 umol, 101.15 uL, 1.5 eq) at 0 °C, then the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with water (3 mL) and extracted with DCM (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 100:1 to 10:1) to give (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide (280 mg, crude) as yellow solid. MS (ESI) *m/z* 522.3 $[M+H]^+$.

[0001972] Step 7: (S)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide

[0001973] To a mixture of (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide (270 mg, 414.13 umol, 80% purity, 1 *eq*) in DCM (3 mL) was added BURGESS REAGENT (197.38 mg, 828.27 umol, 2 *eq*) and stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (0.4 mL) at 20 °C, and then concentrated under reduced pressure (<30 °C) to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 30%-60%, 10 min) to give (S)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamido)-4,4-dimethylpentanamide (104.51 mg, 207.54 umol, 50.12% yield, 100% purity) as white solid. MS (ESI) *m/z* 504.2 $[M+H]^+$.

[0001974] ^1H NMR (400 MHz, DMSO-d_6) δ = 9.09 (br s, 1H), 8.95 (d, *J* = 8.1 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 7.52 (br s, 1H), 5.02 - 4.87 (m, 1H), 4.39 (br s, 1H), 4.33 (br d, *J* = 6.5 Hz, 1H), 3.15 - 3.00 (m, 2H), 2.37 - 2.29 (m, 1H), 2.22 - 2.12 (m, 1H), 1.85 - 1.66 (m, 3H), 1.64 - 1.44 (m, 3H), 1.42 - 1.30 (m, 1H), 0.96 - 0.78 (m, 18H)

Example 235. Synthesis of viral protease inhibitor compound 3065



[0001975] Step 1: (6S,9S,12S)-methyl 6-(tert-butyl)-9-(cyclopropylmethyl)-12-(((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate

[0001976] To a mixture of methyl (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (404.97 mg, 1.75 mmol, 1.2 *eq*) in DCM (3 mL) was added (600 mg, 1.46 mmol, 88% purity, 1 *eq*, HCl), DMAP (534.77 mg, 4.38 mmol, 3 *eq*) and EDCI (559.43 mg, 2.92 mmol, 2 *eq*), then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addtion into water (1 mL), and then extracted with DCM (3 mL * 3). The combined organic layers were washed with HCl (1M, 3 mL), then washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column (SiO_2, DCM:MeOH = 100:1 to 10:1) to give (6S,9S,12S)-methyl 6-(tert-butyl)-9-(cyclopropylmethyl)-12-(((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (550 mg, 969.97 umol, 66.48% yield, 95% purity) as white solid. MS (ESI) *m/z* 539.3 $[M+H]^+$.

[0001977] Step 2: tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate

[0001978] A mixture of (6S,9S,12S)-methyl 6-(tert-butyl)-9-(cyclopropylmethyl)-12-(((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (550 mg, 969.97 umol, 95% purity, 1 *eq*) in NH_3/MeOH (7 M, 5 mL, 39.70 *eq*) was stirred at 60 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (520 mg, crude) as white solid. MS (ESI) *m/z* 524.3 $[M+H]^+$.

[0001979] Step 3: (S)-2-amino-N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-3,3-dimethylbutanamide

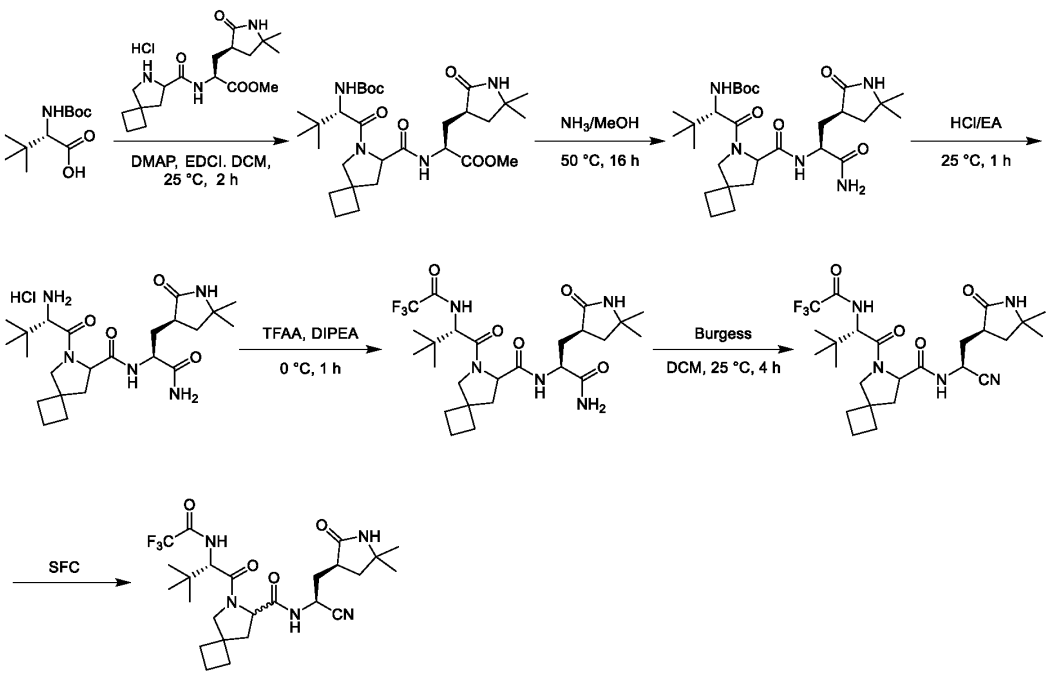
[0001980] A mixture of tert-butyl ((S)-1-(((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (500 mg, 954.81 umol, 1 *eq*) in HCl/EA (4 M, 10 mL) was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give (S)-2-amino-N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-3,3-dimethylbutanamide (350 mg, crude, HCl) as white solid. MS (ESI) *m/z* 424.2 $[M+H]^+$.

[0001981] Step 4: (S)-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamide

[0001982] A mixture of (S)-2-amino-N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-3,3-dimethylbutanamide (300 mg, 586.94 umol, 90% purity, 1 *eq*, HCl) in DCM (1 mL) was added TFAA (160.26 mg, 763.03 umol, 106.13 uL, 1.3 *eq*) and DIEA (227.57 mg, 1.76 mmol, 306.70 uL, 3 *eq*) at 0 °C, then stirred at 20 °C for 1 h. Upon completion, the mixture was quenched with water (1 mL) and concentrated under reduced pressure to give a residue (<30 °C). The residue was purified by prep-HPLC (column: Phenomenex C18 75*30mm*3um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 30%-60%, 12 min) to give (S)-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanamide (40.23 mg, 77.08 umol, 13.13% yield, 96.1% purity) as white solid. MS (ESI) *m/z* 502.2 $[M+H]^+$.

[0001983] ^1H NMR (400 MHz, DMSO-d_6) δ = 9.16 - 9.03 (m, 1H), 8.98 - 8.85 (m, 1H), 8.41 - 8.30 (m, 1H), 7.94 - 7.80 (m, 1H), 5.00 - 4.82 (m, 1H), 4.47 - 4.37 (m, 1H), 4.28 - 4.20 (m, 1H), 2.22 - 2.11 (m, 1H), 2.02 - 1.93 (m, 1H), 1.80 - 1.62 (m, 2H), 1.54 (dd, *J* = 10.1, 12.3 Hz, 1H), 1.39 - 1.28 (m, 1H), 1.25 - 1.20 (m, 1H), 1.20 - 1.16 (m, 3H), 1.10 (s, 3H), 0.93 (s, 9H), 0.76 - 0.62 (m, 1H), 0.46 - 0.29 (m, 2H), 0.17 - 0.01 (m, 2H)

Example 236. Synthesis of viral protease inhibitor compound 3071a



[0001984] Step 1: methyl (2S)-2-[[6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4] octane-7-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[0001985] To a solution of (2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoic acid (206.60 mg, 893.27 umol, 1.1 *eq*) and methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (350 mg, 812.06 umol, 90% purity, 1 *eq*, HCl) in DCM (10 mL) was added DMAP (297.63 mg, 2.44 mmol, 3 *eq*) and EDCI (311.35 mg, 1.62 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with **H_2O 20** mL and extracted with **DCM 45** mL (**15** mL * **3**). The combined organic layers were washed with **brine 20** mL (**20** mL * 1), dried over **Na_2SO_4,** filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, **Petroleum ether/Ethyl acetate = 5/1** to 0/**1**) to give methyl (2S)-2-[[6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (300 mg, 494.06 umol, 60.84% yield, 93% purity) as a white solid. MS (ESI) m/z 565.3 $[M+H]^+$

[0001986] Step2: tert-butyl N-[(1S)-1-[7-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2- oxo-ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carbonyl]-2,2-dimethyl-propyl]carbamate

[0001987] A solution of methyl (2S)-2-[[6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4]octane-7-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (300 mg, 531.24 umol, 1 *eq*) in NH_3/MeOH (7 M, 15.00 mL, 197.65 *eq*) was stirred at 50 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give tert-butyl N-[(1S)-1-[7-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carbonyl]-2,2-dimethyl-propyl]carbamate (290 mg, crude) as a white solid. MS (ESI) m/z 550.3 $[M+H]^+$

[0001988] Step 3: 6-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo- pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6-azaspiro[3.4]octane-7-carboxamide

[0001989] A mixture of tert-butyl N-[(1S)-1-[7-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carbonyl]-2,2-dimethyl-propyl]carbamate (200 mg, 338.37 umol, 93% purity, 1 *eq*) in HCl/EtOAc (4 M, 4.65 mL, 54.97 *eq*) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give 6-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6-azaspiro[3.4]octane-7-carboxamide (176 mg, crude, HCl) as a yellow solid.

[0001990] Step 4: N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6-[(2S)-3,3 -dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide

[0001991] A mixture of 6-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6-azaspiro[3.4]octane-7-carboxamide (120 mg, 246.89 umol, 1 *eq*, HCl) in DCM (2 mL) was added DIPEA (95.73 mg, 740.67 umol, 129.01 uL, 3 *eq*) and TFAA (103.71 mg, 493.78 umol, 68.68 uL, 2 *eq*) at 0 °C, the mixture was stirred at 0 °C for 1 h. Upon completion, the reaction mixture

was quenched by addition **$NaHCO_3$ 4** mL at 25 °C, and extracted with DCM **6** mL (**2** mL * **3**). The combined organic layers were washed with **brine 6** mL (**3** mL * **2**), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide (130 mg, crude) as a yellow solid. MS (ESI) m/z 546.3 $[M+H]^+$

[0001992] Step 5: N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-6-[(2S)-3,3-dimethyl-2- [(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide

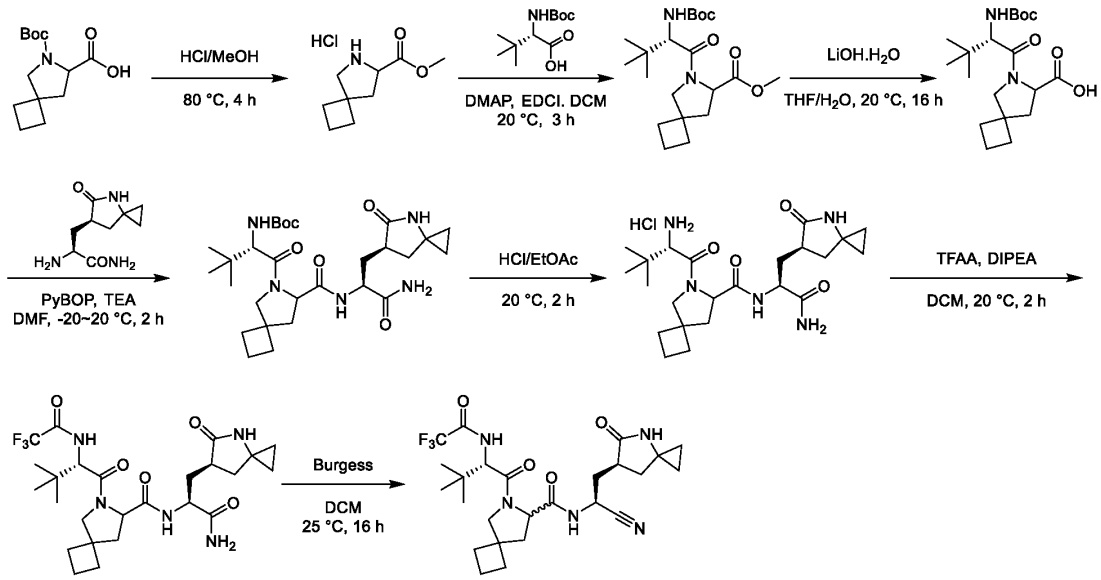
[0001993] A mixture of N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide (180 mg, 170.59 umol, 50% purity, 1 *eq*) in DCM (5 mL) was added Burgess reagent (121.96 mg, 511.77 umol, 3 *eq*), the mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition;column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-65%,8min) to give desired product (50 mg) as a white solid, which was further separated by SFC (condition:column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 35%-35%,15min) to give N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide (Isomer 1, 20 mg, 37.53 umol, 22.00% yield, 99% purity) as a white solid. MS (ESI) m/z 528.2 $[M+H]^+$

[0001994] ^1H NMR (400 MHz, DMSO-d_6) δ = 9.36 - 9.14 (m, 1H), 8.83 (d, J = 8.2 Hz, 1H), 7.82 (s, 1H), 4.98 - 4.84 (m, 1H), 4.51 (s, 1H), 4.18 (t, J = 8.0 Hz, 1H), 3.87 (d, J = 9.9 Hz, 1H), 3.49 (d, J = 10.1 Hz, 1H), 2.62 - 2.56 (m, 1H), 2.29 - 2.09 (m, 2H), 2.06 - 1.80 (m, 7H), 1.77 - 1.67 (m, 2H), 1.58 - 1.50 (m, 1H), 1.20 - 1.06 (m, 6H), 1.05 - 0.87 (m, 9H)

[0001995] To give N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide (Isomer 2, 20 mg, 37.30 umol, 21.87% yield, 98.4% purity) as a white solid. MS (ESI) m/z 528.2 $[M+H]^+$

[0001996] ^1H NMR (400 MHz, DMSO-d_6) δ = 9.54 - 9.35 (m, 1H), 8.56 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H), 5.04 - 4.87 (m, 1H), 4.67 (br d, J = 8.2 Hz, 1H), 4.19 (t, J = 7.4 Hz, 1H), 3.83 (d, J = 10.4 Hz, 1H), 3.60 (d, J = 10.1 Hz, 1H), 2.52 (br s, 1H), 2.25 (dd, J = 8.3, 12.5 Hz, 1H), 2.10 - 1.68 (m, 10H), 1.58 - 1.44 (m, 1H), 1.23 - 1.08 (m, 6H), 0.97 (s, 9H).

Example 237. Synthesis of viral protease inhibitor compound 3039a



[0001997] Step 1: methyl 6-azaspiro[3.4]octane-7-carboxylate

[0001998] To a solution of 6-tert-butoxycarbonyl-6-azaspiro[3.4]octane-7-carboxylic acid (0.3 g, 1.18 mmol, 1 eq) in 4 M of HCl/MeOH (5 mL). Then the reaction was stirred at 80 °C for 4 h. Upon completion, the reaction was concentrated in vacuo to dryness give methyl 6-azaspiro[3.4]octane-7-carboxylate (240 mg, crude, HCl) was obtained as a brown solid. The crude product was used directly in next step.

[0001999] Step 2: methyl 6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4]octane-7-carboxylate

[0002000] To a solution of methyl 6-azaspiro[3.4]octane-7-carboxylate (240 mg, 1.17 mmol, 1 eq, HCl) in DCM (5 mL) was added (2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoic acid (323.85 mg, 1.40 mmol, 1.2 eq), DMAP (285.11 mg, 2.33 mmol, 2 eq). Then the reaction was added EDCI (447.37 mg, 2.33 mmol, 2 eq) at 20 °C. Then the reaction was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was quenched by addition 1 N HCl 30 mL at 20 °C, and then diluted with EtOAc 20 mL and extracted with EtOAc 60 mL (20 mL * 3). The combined organic layers were washed with sat. $NaHCO_3$ 40 mL (20 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 15/1) to give methyl 6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4]octane-7-carboxylate (300 mg, 784.33 umol, 67.22% yield, assumed 100% purity) as a colorless oil.

[0002001] Step 3: 6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4]octane-7-carboxylic acid

[0002002] To a solution of methyl 6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4]octane-7-carboxylate (300 mg, 784.33 umol, 1 eq) in THF (1.5 mL) and H_2O (0.5 mL) was added $LiOH.H_2O$ (98.74 mg, 2.35 mmol, 3 eq). Then the reaction was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was quenched by additional EtOAc 5 mL at 20 °C, and then diluted with H_2O 20 mL. Then seperated the aquire phase adjusted pH=1 by 1 M HCl and extracted with EtOAc 15 mL (5 mL * 3). The combined organic layers were washed with sat. $NaHCO_3$ 5 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue of 6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4]octane-7-carboxylic acid (270 mg, crude) as a colorless gum. The crude product was used directly in next step.

[0002003] Step 4: tert-butyl N-[(1S)-1-[7-[[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carbonyl]-2,2-dimethyl-propyl]carbamate

[0002004] To a solution of 6-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6-azaspiro[3.4]octane-7-carboxylic acid (210 mg, 569.93 umol, 1 eq) and (2S)-2-amino-3-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]propanamide (112.41 mg, 569.93 umol, 1 eq) in DMF (2 mL) was added PyBOP (296.59 mg, 569.93 umol, 1 eq) and TEA (115.34 mg, 1.14 mmol, 158.66 uL, 2 eq) in DMF (1 mL) at -20 °C. Then the reaction was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O 20 mL and extracted with EtOAc 30 mL (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 0/1, 10% MeOH) give the compound of tert-butyl N-[(1S)-1-[7-[[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carbonyl]-2,2-dimethyl-propyl]carbamate (175 mg, 319.53 umol, 56.06% yield, assumed 100% purity) was obtained as a white oil.

[0002005] Step 5: 6-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide

[0002006] To a solution of tert-butyl N-[(1S)-1-[7-[[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carbonyl]-2,2-dimethyl-propyl]carbamate (140 mg, 255.62 umol, 1 eq) in 4 M of HCl/EtOAc (5 mL). Then the reaction was stirred at 20 °C for 2 h. Upon completion, the reaction was concentrated in vacuo to dryness give the compound of 6-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide (133 mg, crude, 2HCl) as a white solid. The crude product was used directly in next step.

[0002007] Step 6: N-[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide

[0002008] To a solution of 6-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]-6-azaspiro[3.4]octane-7-carboxamide (133 mg, 255.53 umol, 1 eq, 2HCl) in DCM (3 mL) was added DIEA

(132.10 mg, 1.02 mmol, 178.03 uL, 4 eq), then added TFAA (134.17 mg, 638.82 umol, 88.86 uL, 2.5 eq) in DCM (0.5 mL). Then the reaction was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 10 mL at 20 °C, and then diluted with EtOAc 10 mL and extracted with EtOAc 20 mL (10 mL * 2). The combined organic layers were washed with sat. NaCl 10 mL (10 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound N-[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide (110 mg, crude) as brown solid. The crude product was used directly in next step.

[0002009] Step 7: N-[(1S)-1-cyano-2-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide

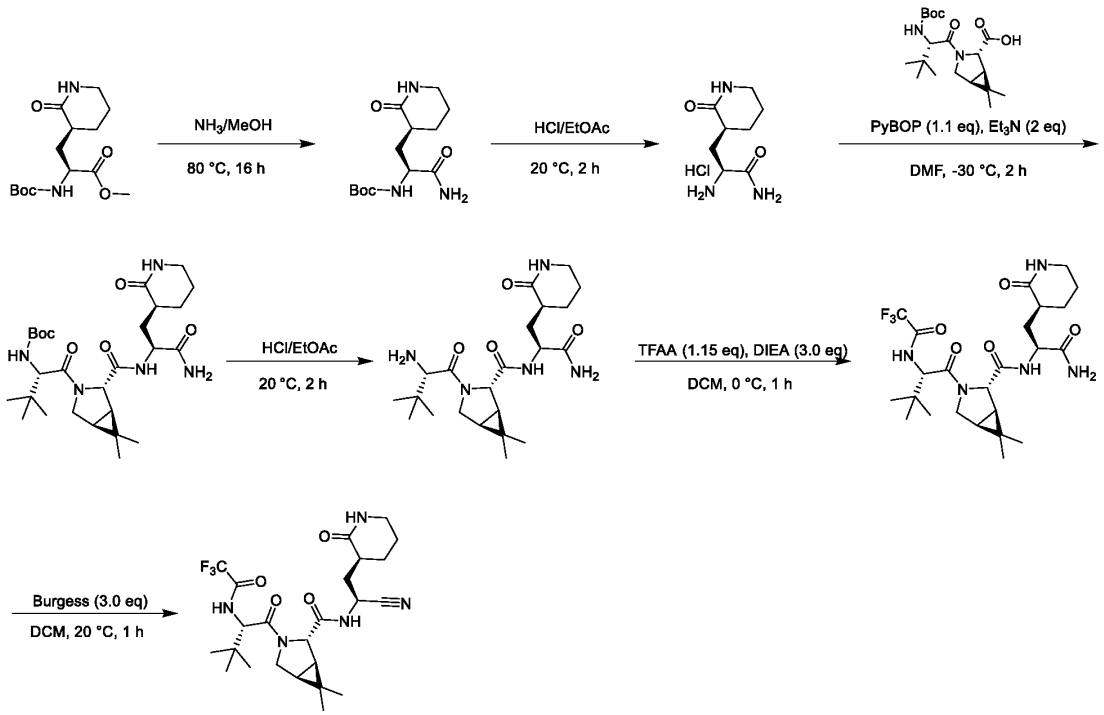
[0002010] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide (110 mg, 202.36 umol, 1 eq) in DCM (5 mL) was added BURGESS REAGENT (106.09 mg, 445.20 umol, 2.2 eq). Then the reaction was stirred at 25 °C for 16 h. Upon completion, the reaction was blow-dried by N_2. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 35%-55%,8min), and prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(FA)-ACN];B%: 45%-75%,8min) to give N-[(1S)-1-cyano-2-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide (Isomer 1, 10 mg, 18.63 umol, 9.21% yield, 97.9% purity) as white solid. MS (ESI) m/z 526.1 $[M+H]^+$.

[0002011] ^1H NMR (400 MHz, DMSO-d_6) δ = 9.41 (br d, J = 9.0 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H), 5.03 - 4.80 (m, 1H), 4.67 (d, J = 8.8 Hz, 1H), 4.19 (t, J = 7.3 Hz, 1H), 3.83 (d, J = 10.3 Hz, 1H), 3.61 (d, J = 10.3 Hz, 1H), 2.58 - 2.52 (m, 1H), 2.25 (dd, J = 8.3, 12.5 Hz, 1H), 2.11 - 1.92 (m, 5H), 1.91 - 1.75 (m, 6H), 0.97 (s, 9H), 0.79 - 0.69 (m, 1H), 0.63 - 0.48 (m, 3H).

[0002012] To give N-[(1S)-1-cyano-2-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]ethyl]-6-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6-azaspiro[3.4]octane-7-carboxamide (Isomer 2, 20 mg, 34.40 umol, 17.00% yield, 90.4% purity) as white solid. MS (ESI) m/z 526.2 $[M+H]^+$.

[0002013] ^1H NMR (400 MHz, DMSO-d_6) δ = 9.35 (br d, J = 7.1 Hz, 1H), 8.89 (d, J = 8.7 Hz, 1H), 7.73 (s, 1H), 5.04 - 4.82 (m, 1H), 4.52 (br d, J = 5.9 Hz, 1H), 4.18 (t, J = 8.1 Hz, 1H), 3.88 (d, J = 9.9 Hz, 1H), 3.49 (d, J = 10.0 Hz, 1H), 2.76 - 2.68 (m, 1H), 2.28 - 2.15 (m, 2H), 2.05 - 1.92 (m, 4H), 1.86 (br d, J = 2.8 Hz, 4H), 1.80 - 1.65 (m, 2H), 1.00 (s, 9H), 0.79 - 0.67 (m, 1H), 0.63 - 0.47 (m, 3H).

Example 238. Synthesis of viral protease inhibitor compound 3133



[0002014] Step 1: tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamate

[0002015] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (5 g, 16.65 mmol, 1 *eq*) in NH_3/MeOH (7 M, 50 mL, 21.02 *eq*) was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under

reduced pressure to give a residue. Then the mixture was dissolved in DCM (10 mL) and concentrated under reduced pressure for two times to give tert-butyl N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamate (10.1 g, crude) was obtained as a white solid and used directly next step. MS (ESI) *m/z* 286.1 $[M+H]^+$

[0002016] Step 2: (S)-2-amino-3-((S)-2-oxopiperidin-3-yl)propanamide

[0002017] A mixture of tert-butyl N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamate (10.1 g, 35.40 mmol, 1 *eq*) in HCl/EtOAc (4 M, 151.50 mL, 17.12 *eq*) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. Then the mixture was dissolved in toluene (10 mL) and concentrated under reduced pressure for two times to give methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanamide (10.1 g, crude) as a light yellow solid which was used directly next step. MS (ESI) *m/z* 186.2 $[M+H]^+$

[0002018] Step 3: methyl ((4-(tert-butyl)phenyl)(2-((4,4-difluorocyclohexyl)amino)-1-(5-fluoropyridin-3-yl)-2-oxoethyl)carbamoyl)-L-prolinate

[0002019] To a solution of (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanamide (0.5 g, 2.26 mmol, 1 *eq*, HCl) and (1R,2S,5S)-3-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (831.06 mg, 2.26 mmol, 1 *eq*) in DMF (10 mL) was added PyBOP (1.29 g, 2.48 mmol, 1.1 *eq*) and then added Et_3N (456.46 mg, 4.51 mmol, 627.86 uL, 2 *eq*). The mixture was stirred at -30 °C for 2 h. Upon completion, the combined reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (40 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate/MeOH = 20/1/0 to 0/0/1) to give tert-butyl N-[(1S)-1-[(1R,2S,5S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carbonyl]-2,2-dimethyl-propyl]carbamate (290 mg, 541.37 umol, 24.00% yield) as a light yellow solid. MS (ESI) *m/z* 436.2 $[M-100+H]^+$

[0002020] Step 4: (1R,2S,5S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-((S)-2-amino-3,3-dimethylbutanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

[0002021] A mixture of tert-butyl N-[(1S)-1-[(1R,2S,5S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carbonyl]-2,2-dimethyl-propyl]carbamate (290 mg, 541.37 umol, 1 *eq*) in HCl/EtOAc (4 M, 50 mL, 369.43 *eq*) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. Then the mixture was dissolved in toluene (10 mL) and concentrated under reduced pressure for two times to give (1R,2S,5S)-3-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (300 mg, crude, HCl) was obtained as a yellow solid and used directly next step.

[0002022] Step 5: (1R,2S,5S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

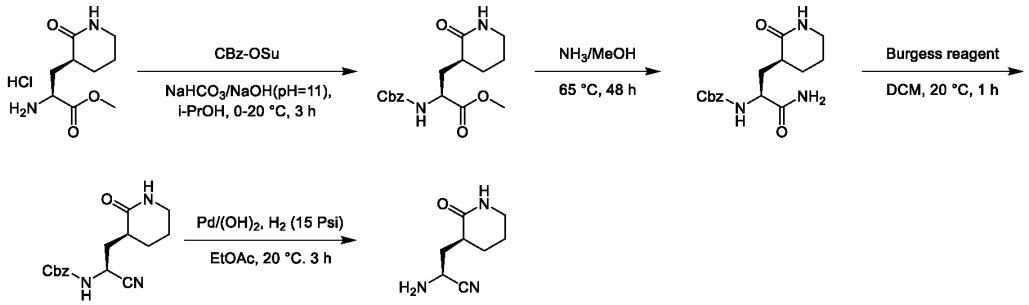
[0002023] To a solution of (1R,2S,5S)-3-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (0.2 g, 423.71 umol, 1 eq, HCl) in DCM (10 mL) was added DIEA (164.29 mg, 1.27 mmol, 221.41 uL, 3 eq) and TFAA (102.34 mg, 487.27 umol, 67.78 uL, 1.15 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h. Upon completion, the combined reaction mixture was poured into aq. $NaHCO_3$ (20 mL) and extracted with DCM (10 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (1R,2S,5S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (294 mg, crude) as a yellow solid which was used directly next step. MS (ESI) *m/z* 532.2 $[M+H]^+$

[0002024] Step 6: (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

[0002025] To a solution of (1R,2S,5S)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (194 mg, 364.96 umol, 1 *eq*) in DCM (10 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (260.91 mg, 1.09 mmol, 3 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by water (0.5 mL) at 20 °C, and the system was blow-dried with N_2 to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250 * 50 mm * 10um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 50%, 10 min) to give (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (60.22 mg, 117.26 umol, 32.13% yield, 100% purity) as a white solid. MS (ESI) *m/z* 514.2 $[M+H]^+$

[0002026] ^1H NMR (400MHz, DMSO-d_6) δ = 9.41 (br d, *J* = 7.2 Hz, 1H), 8.99 (d, *J* = 8.3 Hz, 1H), 7.51 (s, 1H), 5.01 (ddd, *J* = 5.9, 8.4, 10.2 Hz, 1H), 4.44 - 4.38 (m, 1H), 4.16 (s, 1H), 3.90 (dd, *J* = 5.5, 10.3 Hz, 1H), 3.68 (d, *J* = 10.5 Hz, 1H), 3.12 - 3.05 (m, 2H), 2.37 - 2.19 (m, 2H), 1.85 (br dd, *J* = 3.7, 12.7 Hz, 1H), 1.79 - 1.66 (m, 2H), 1.60 - 1.52 (m, 2H), 1.43 - 1.33 (m, 1H), 1.29 (d, *J* = 7.7 Hz, 1H), 1.02 (s, 3H), 0.99 (s, 9H), 0.84 (s, 3H).

Example 239. Synthesis of (S)-2-amino-3-((S)-2-oxopiperidin-3-yl)propanenitrile



Step 1: (S)-methyl 2-(((benzyloxy)carbonyl)amino)-3-((S)-2-oxopiperidin-3-yl)propanoate

[0001] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (10 g, 38.02 mmol, 90% purity, 1 eq, HCl) in IPA (100 mL) was added a solution of pH=11 of NaOH (4 M, 10.00 mL, 1.05 *eq*) and $NaHCO_3$ (194.40 g, 2.31 mol, 90.00 mL, 60.86 *eq*) at 0 °C. Then benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (10.42 g, 41.83 mmol, 1.1 *eq*) was added. The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was poured into H_2O 100 mL at 20 °C, and then extracted with EtOAc (100mL * 3). The combined organic layers were washed with brine (100 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=80/1 to 30/1) to give methyl (2S)-2-(benzyloxycarbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (10.5 g, 31.40 mmol, 82.59% yield) as a yellow oil.

Step 2: benzyl ((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamate

[0002] A solution of methyl (2S)-2-(benzyloxycarbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (10 g, 14.95 mmol, 1 eq) in NH_3/MeOH (7 M, 50 mL, 23.41 eq) was stirred at 65 °C for 48 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove MeOH to give benzyl N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamate (9.55 g, crude) as a yellow solid.

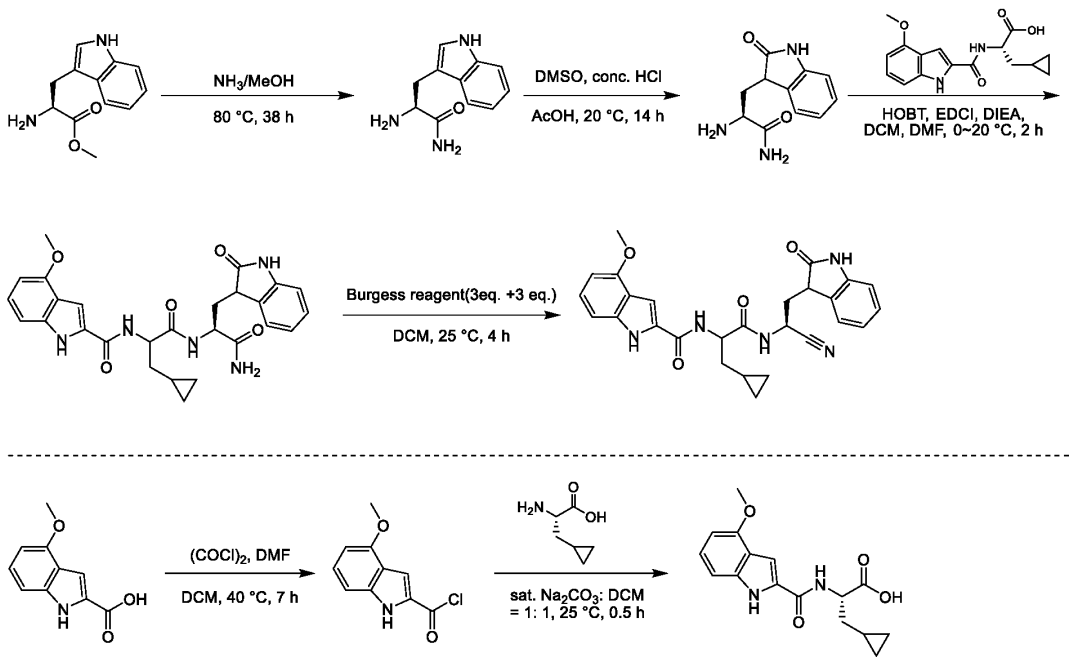
Step 3: benzyl ((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)carbamate

[0003] To a solution of benzyl N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamate (9.55 g, 29.90 mmol, 1 eq) in DCM (100 mL) was added Burgess reagent (14.25 g, 59.81 mmol, 2 eq). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was poured into H_2O 120 mL at 20 °C, and then extracted with DCM (120 mL * 3). The combined organic layers were washed with brine (100 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0/1) to give benzyl N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamate (7.4 g, 24.56 mmol, 82.12% yield) as a yellow oil.

Step 4: (S)-2-amino-3-((S)-2-oxopiperidin-3-yl)propanenitrile

[0004] To a solution of benzyl N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamate (300 mg, 995.55 umol, 1 eq) in IPA (6 mL) was added Pd(OH)2 (699.05 mg, 995.55 umol, 20% purity, 1 eq). The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH=1/0 to 80/1) to give (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanenitrile (147 mg, 820.24 umol, 82.39% yield, 93.3% purity) as a white solid. MS (ESI) m/z 168.1 $[M+H]^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ = 4.11 (t, J = 7.9 Hz, 1H), 3.30 - 3.23 (m, 2H), 2.56 - 2.45 (m, 1H), 2.27 - 2.15 (m, 1H), 2.03 (d, J = 3.0, 6.3, 12.9 Hz, 1H), 1.92 - 1.84 (m, 1H), 1.81 - 1.70 (m, 2H), 1.64 - 1.51 (m, 1H).

Example 240. Synthesis of viral protease inhibitor compound 247



Step 1: (S)-2-amino-3-(1H-indol-3-yl)propanamide

[0005] A solution of methyl (2S)-2-amino-3-(1H-indol-3-yl)propanoate (20 g, 78.52 mmol, 1 *eq*, HCl) in NH_3/MeOH (7 M, 200.00 mL, 17.83 *eq*) was stirred at 80 °C for 38 h. Upon completion, the reaction mixture was concentrated under reduced pressure

to give (S)-2-amino-3-(1H-indol-3-yl)propanamide (17 g, crude) as a yellow solid. MS (ESI) *m/z* 204.1 $[M+H]^+$.

Step 2: (2S)-2-amino-3-(2-oxoindolin-3-yl)propanamide

[0006] To a mixture of (2S)-2-amino-3-(1H-indol-3-yl)propanamide (17 g, 83.64 mmol, 1 *eq*) in AcOH (170 mL) was slowly added a mixture of HCl (12 M, 27.88 mL, 4 *eq*) and DMSO (9.80 g, 125.47 mmol, 9.80 mL, 1.5 eq), and then the mixture was stirred at 20 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove HCl and AcOH, then was quenched by addition $NH_3.H_2O$ until adjust to pH>8 at 20 °C. The residue was purified by prep-HPLC (column: Xtimate C18 10u 250 mm* 80 mm; mobile phase: [water(0.05%NH_3H_2O+10 mM NH_4HCO_3)-ACN]; B%: 0%-20%, 30 min) to give (2S)-2-amino-3-(2-oxoindolin-3-yl)propanamide (3.0 g, 10.95 mmol, 13.09% yield, 80% purity) as yellow solid. MS (ESI) *m/z* 220.2 $[M+H]^+$.

Step 3: 4-methoxy-1H-indole-2-carbonyl chloride

[0007] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (10 g, 52.31 mmol, 1 *eq*) in DCM (100 mL) was added $(COCl)_2$ (26.56 g, 209.22 mmol, 18.31 mL, 4 *eq*) and DMF (191.16 mg, 2.62 mmol, 201.22 uL, 0.05 *eq*), then was stirred at 40 °C for 5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give 4-methoxy-1H-indole-2-carbonyl chloride (11 g, crude) as brown solid.

Step 4: (S)-3-cyclopropyl-2-(4-methoxy-1H-indole-2-carboxamido)propanoic acid

[0008] To a mixture of (2S)-2-amino-3-cyclopropyl-propanoic acid (9.49 g, 73.46 mmol, 1.4 *eq*) in DCM (100 mL) and sat.Na_2CO_3 (50 mL) was dropwise added a solution of 4-methoxy-1H-indole-2-carbonyl chloride (11 g, 52.47 mmol, 1 *eq*) in DCM (100 mL) at 25 °C. Then the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was adjusted with 1 N HCl to pH=1, then extracted with DCM (50 mL* 3). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure and purifired with prep-HPLC(column: Phenomenex luna C18 (250* 70 mm,15 um); mobile phase: [water(0.05%HCl)-ACN]; B%: 23%-53%, 27 min) to give (S)-3-cyclopropyl-2-(4-methoxy-1H-indole-2-carboxamido)propanoic acid (8.0 g, 23.82 mmol, 45.39% yield, 90% purity) as yellow solid. MS (ESI) *m/z* 303.1 $[M+H]^+$.

Step 5: N-(1-(((2S)-1-amino-1-oxo-3-(2-oxoindolin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

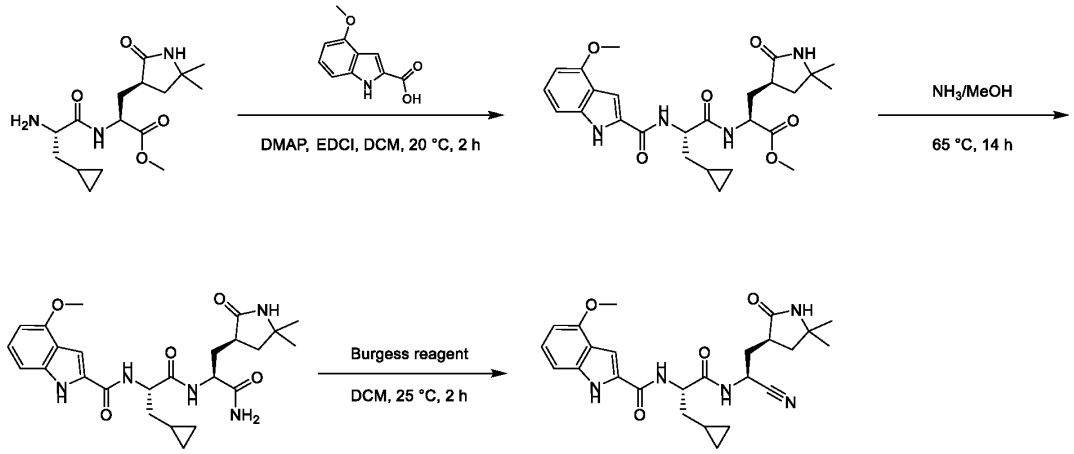
[0009] To a solution of (2S)-2-amino-3-(2-oxoindolin-3-yl)propanamide (2 g, 7.30 mmol, 80% purity, 1 *eq*) in DCM (20 mL) and DMF (5 mL) was added (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (2.75 g, 7.30 mmol, 90% purity, 1 *eq*, HCl), DIEA (1.89 g, 14.60 mmol, 2.54 mL, 2 *eq*), HOBt (1.97 g, 14.60 mmol, 2 *eq*), and then EDCI (2.80 g, 14.60 mmol, 2 *eq*) at 0 °C. The mixture was then stirred at 20 °C for 2 h. The reaction mixture was quenched by addition H_2O (1 mL) at 20 °C, then concentrated under reduced pressure and purified by prep-HPLC (column: Phenomenex luna C18 (250* 70 mm,15 um); mobile phase: [water(0.05% HCl)-ACN]; B%: 22%-52%, 27 min) to give N-(1-(((2S)-1-amino-1-oxo-3-(2-oxoindolin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (2.5 g, 4.87 mmol, 66.67% yield, 98% purity) as yellow solid. MS (ESI) *m/z* 504.2 $[M+H]^+$.

Step 6: N-(1-(((1S)-1-cyano-2-(2-oxoindolin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[00010] To a mixture of N-(1-(((2S)-1-amino-1-oxo-3-(2-oxoindolin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (2.5 g, 4.87 mmol, 98% purity, 1 *eq*) in DCM (25 mL) was added Burgess reagent (3.48 g, 14.60 mmol, 3 *eq*) and stirred at 20 °C for 2 h. Then was added Burgess reagent (3.48 g, 14.60 mmol, 3 *eq*) and stirred at 20 °C for 2 h. The reaction mixture was quenched by addition H_2O (2.5 mL) at 20 °C, then concentrated under reduced pressure (<30°C) and purified by prep-HPLC (column: Agela DuraShell C18 250* 70 mm* 10 um; mobile phase: [water(0.225%FA)-ACN]; B%: 30%-60%, 20 min) to give N-(1-(((1S)-1-cyano-2-(2-oxoindolin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (800 mg, 1.59 mmol, 32.65% yield, 96.4% purity) as white solid. MS (ESI) *m/z* 486.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.55 (br d, J = 11.0 Hz, 1H), 10.52 (br d, J = 18.5 Hz, 1H), 9.13 - 8.94 (m, 1H), 8.51 (br d, J = 6.9 Hz, 1H), 7.36 (br s, 1H), 7.33 - 7.24 (m, 1H), 7.22 - 7.15 (m, 1H), 7.13 - 7.05 (m, 1H), 7.02 - 6.91 (m, 2H), 6.84 (br t, J = 6.1 Hz, 1H), 6.50 (br d, J = 7.0 Hz, 1H), 5.32 - 5.02 (m, 1H), 4.59 - 4.40 (m, 1H), 3.88 (br s,

3H), 3.52 - 3.46 (m, 1H), 2.41 - 2.15 (m, 2H), 1.90 - 1.67 (m, 1H), 1.64 - 1.35 (m, 1H), 0.91 - 0.70 (m, 1H), 0.53 - 0.31 (m, 2H), 0.27 - 0.00 (m, 2H)

Example 241. Synthesis of viral protease inhibitor compound 689



Step 1: (S)-methyl 2-((S)-3-cyclopropyl-2-(4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[00011] A solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (150 mg, 460.97 umol, 1 eq), 4-methoxy-1H-indole-2-carboxylic acid (105.76 mg, 553.16 umol, 1.2 eq) in DCM (5 mL) was added DMAP (112.63 mg, 921.94 umol, 2 eq) and EDCI (132.55 mg, 691.45 umol, 1.5 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 10 mL, and then extracted with DCM (10 mL * 3). The combined organic layers were washed with brine 15 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (125 mg, 248.21 umol, 53.85% yield, 99% purity) as yellow oil. MS (ESI) m/z 499.2 $[M+H]^+$.

Step 2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

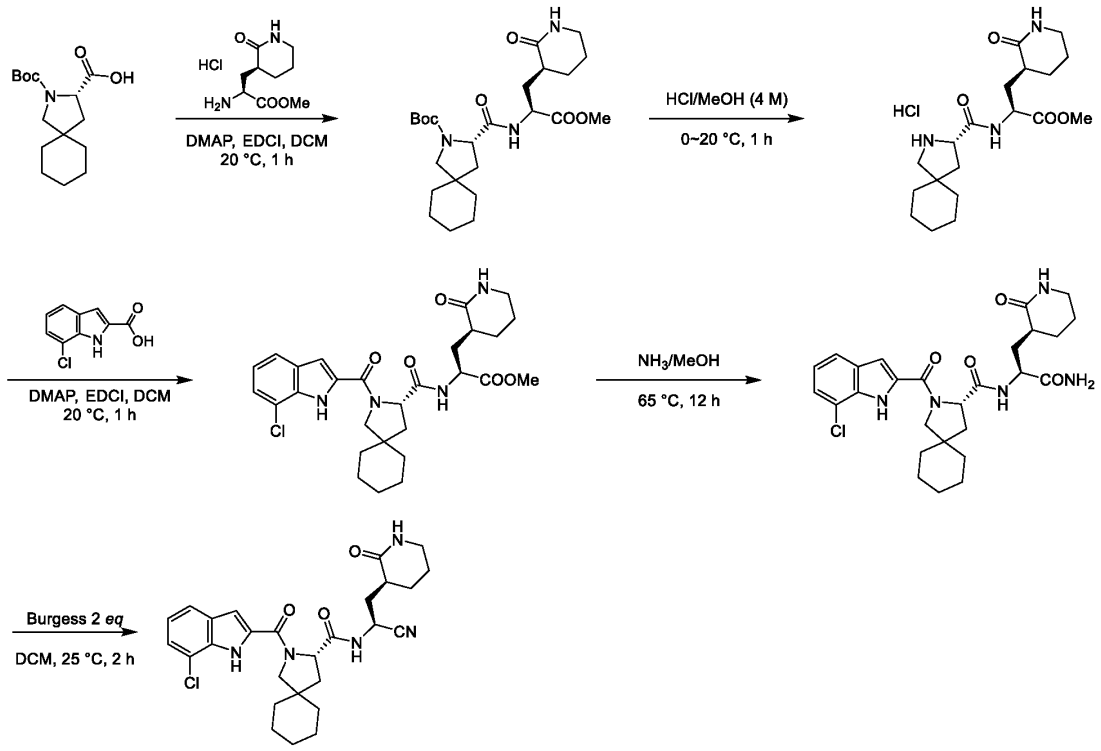
[00012] A solution of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl) amino] propanoyl] amino]-3-[(3R)-5, 5-dimethyl-2-oxo-pyrrolidin-3-yl] propanoate (110 mg, 220.63 umol, 1 eq) in NH_3MeOH (220.63 umol, 10 mL, 1 eq)

was stirred at 65 °C for 14 h. Upon completion, the mixture was concentrated under reduce pressure to remove NH_3MeOH. DCM (10 mL) (three times) was added and the resulting solution was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (105 mg, crude) as a white solid. MS (ESI) m/z 484.2 $[M+H]^+$.

Step 3: N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[00013] To a solution of N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (105 mg, 217.14 umol, 1 eq) in DCM (5 mL) was added Burgess reagent (113.84 mg, 477.71 umol, 2.2 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the DCM was removed under N_2. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; 35%-65%, 10 min) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (26 mg, 55.85 umol, 25.72% yield, 100% purity) as a white solid. MS (ESI) m/z 466.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.55 (s, 1H), 8.91 (d, J = 8.2 Hz, 1H), 8.51 (br d, J = 7.6 Hz, 1H), 7.82 (s, 1H), 7.36 (d, J = 1.3 Hz, 1H), 7.13 - 7.06 (m, 1H), 7.03 - 6.98 (m, 1H), 6.50 (d, J = 7.7 Hz, 1H), 5.00 - 4.92 (m, 1H), 4.49 - 4.41 (m, 1H), 3.88 (s, 3H), 2.64 - 2.55 (m, 1H), 2.22 - 2.13 (m, 1H), 1.99 (dd, J = 8.5, 12.3 Hz, 1H), 1.89 - 1.70 (m, 2H), 1.57 - 1.42 (m, 2H), 1.19 - 1.03 (m, 6H), 0.80 (br dd, J = 6.0, 7.3 Hz, 1H), 0.47 - 0.33 (m, 2H), 0.25 - 0.03 (m, 2H)

Example 242. Synthesis of viral protease inhibitor compound 731



Step 1: tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate

[00014] To a mixture of 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (200 mg, 564.65 umol, 80% purity, 1 *eq*) in DCM (3 mL) was added methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (133.65 mg, 564.65 umol, 1 *eq*, HCl), DMAP (206.95 mg, 1.69 mmol, 3 *eq*) and EDCI (216.49 mg, 1.13 mmol, 2 *eq*) at 0 °C, then stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by the addition of water (3 mL), and then was extracted with DCM (3 mL * 3). The combined organic layers were washed with HCl (1M, 3 mL), then washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to afford tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate (200 mg, 429.57 umol, 76.08% yield) as yellow solid. MS (ESI) *m/z* 466.2 $[M+H]^+$.

Step 2: (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate

[00015] A mixture of (tert-butyl 3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate(200 mg, 386.61 umol, 90% purity, 1 *eq*) in HCl/MeOH (4 M, 2.67 mL, 27.59 *eq*) at 0 °C was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate (170 mg, crude, HCl) as yellow solid. MS (ESI) *m/z* 366.1 $[M+H]^+$.

Step 3: (2S)-methyl 2-(2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00016] To a mixture of methyl (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate (172 mg, 427.94 umol, 1 *eq*, HCl) in DCM (3 mL) was added 7-chloro-1H-indole-2-carboxylic acid (83.71 mg, 427.94 umol, 1 *eq*), DMAP (156.84 mg, 1.28 mmol, 3 *eq*) and EDCI (164.07 mg, 855.88 umol, 2 *eq*) at 0 °C, and then the resulting mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by the addition of water (3 mL), and then extracted with DCM (3 mL * 3). The combined organic layers were washed with HCl (1M, 3 mL), then washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give (2S)-methyl 2-(2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (100 mg, 178.80 umol, 41.78% yield, 97.1% purity) as yellow solid. MS (ESI) *m/z* 543.2 $[M+H]^+$.

Step 4: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

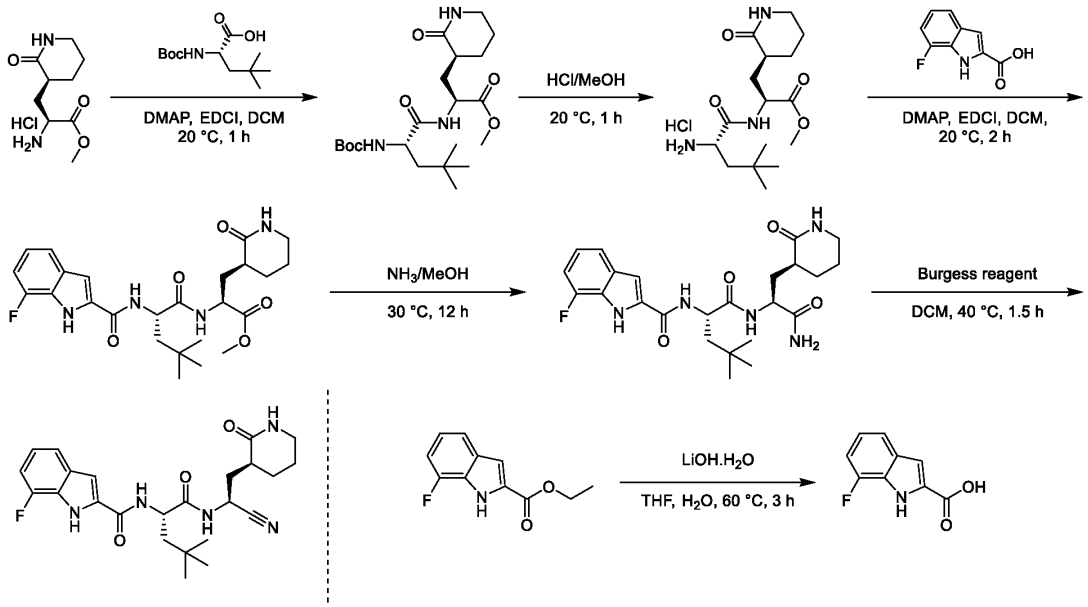
[00017] To a mixture of methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (100 mg, 184.14 umol, 1 *eq*) was added NH_3/MeOH (7 M, 3 mL, 114.04 *eq*), and then the resulting mixture was stirred at 65 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-

azaspiro[4.5]decane-3-carboxamide (90 mg, crude) as yellow solid. MS (ESI) *m/z* 528.2 $[M+H]^+$

Step 5: 2-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[00018] To a mixture of N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (80 mg, 151.50 umol, 1 *eq*) in DCM (3 mL) was added Burgess reagent (72.21 mg, 303.01 umol, 2 *eq*) and stirred at 25 °C for 2 h. Upon completion, the mixture was quenched with water (1 mL) and concentrated under reduced pressure to give a residue (<30 °C). The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-65%, 8min) to give 2-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (4 mg, 7.47 umol, 4.93% yield, 95.2% purity) as white solid. MS (ESI) *m/z* 510.1 $[M+H]^+$. 1H NMR (400 MHz, METHANOL-*d*4) δ = 7.63 (br d, J = 7.9 Hz, 1H), 7.33 - 7.21 (m, 1H), 7.20 - 6.75 (m, 2H), 5.16 - 5.05 (m, 1H), 4.73 - 4.55 (m, 1H), 3.99 - 3.83 (m, 1H), 3.72 (br d, J = 10.5 Hz, 1H), 3.28 - 2.93 (m, 2H), 2.73 - 2.39 (m, 2H), 2.39 - 2.23 (m, 1H), 2.03 (br s, 1H), 1.98 - 1.89 (m, 1H), 1.85 - 1.37 (m, 14H).

Example 243. Synthesis of viral protease inhibitor compound 818



Step 1: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido) -3-((S)-2-oxopiperidin-3-yl)propanoate

[00019] To a solution of methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 3.80 mmol, 90% purity, 1 eq, HCl) and (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (932.77 mg, 3.80 mmol, 1 eq) in DCM (20 mL) was added DMAP (1.16 g, 9.51 mmol, 2.5 eq) and EDCI (1.46 g, 7.60 mmol, 2 eq), and then the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O 50 mL and extracted with DCM (30 mL * 3). The combined organic layers were washed with birne 40 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 0:1) to give the methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.2 g, 2.81 mmol, 73.82% yield) as a white solid. MS (ESI) *m/z* 428.3 $[M+H]^+$.

Step 2: (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00020] A mixture of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.2 g, 2.81 mmol, 1 eq) in HCl/MeOH (4 M, 20 mL, 28.50 eq) was stirred at 20 °C for 1 h. Upon completion,

the reaction mixture was concentrated under reduced pressure to give the methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, crude, HCl) as a white solid.

Step 3: 7-fluoro-1H-indole-2-carboxylic acid

[00021] To a solution of ethyl 7-fluoro-1H-indole-2-carboxylate (900 mg, 4.34 mmol, 1 eq) in THF (10 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (546.77 mg, 13.03 mmol, 3 eq), and then the mixture was stirred at 60 °C for 3 h. Upon completion, the reaction mixture was quenched by addition H_2O 60 mL at 0°C and added drop-wise 1M HCl to pH = 5, and then extracted with ethyl acetate (40 mL * 3). The combined organic layers were washed with brine 30 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the 7-fluoro-1H-indole-2-carboxylic acid (700 mg, crude) as a yellow solid.

Step 4: (S)-methyl 2-((S)-2-(7-fluoro-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00022] To a solution of 7-fluoro-1H-indole-2-carboxylic acid (443.09 mg, 2.47 mmol, 1 eq) and methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.9 g, 2.47 mmol, 1 eq, HCl) in DCM (30 mL) was added DMAP (755.41 mg, 6.18 mmol, 2.5 eq) and EDCI (948.29 mg, 4.95 mmol, 2 eq), and then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O 60 mL and extracted with DCM (40 mL * 3). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 0:1) to give the methyl (2S)-2-[[(2S)-2-[(7-fluoro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.8 g, 1.64 mmol, 66.21% yield) as a white solid. MS (ESI) *m/z* 489.3 $[M+H]^+$

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-fluoro-1H-indole-2-carboxamide

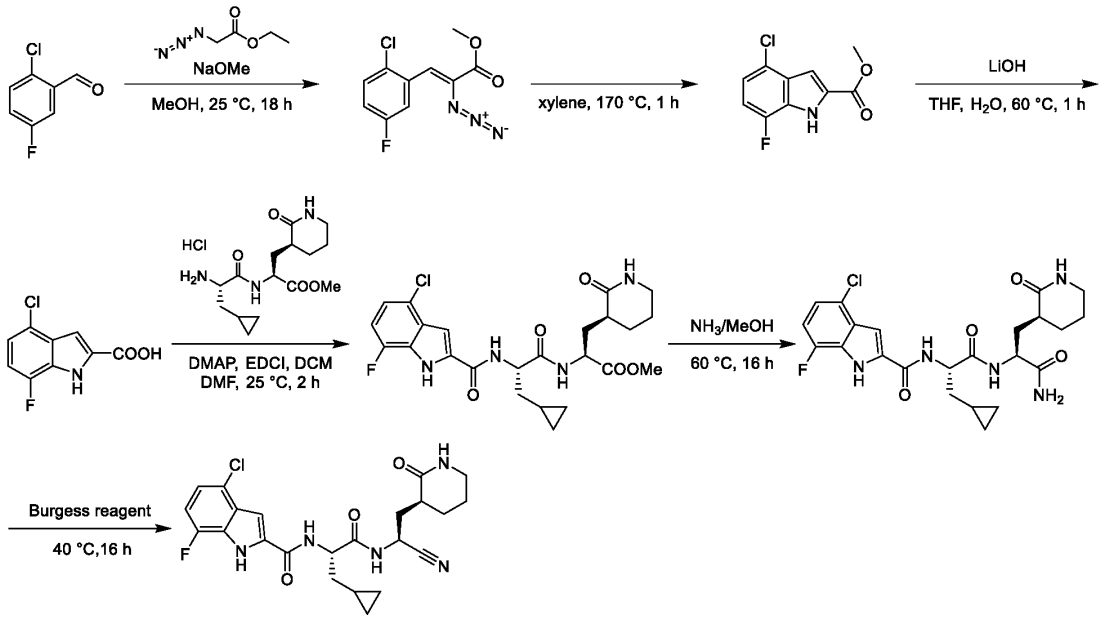
[00023] A mixture of methyl (2S)-2-[[(2S)-2-[(7-fluoro-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.8 g, 1.64 mmol, 1 eq) in NH_3/MeOH (7 M, 20 mL, 85.50 eq), the mixture was stirred at 30 °C

for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-fluoro-1H-indole-2-carboxamide (0.7 g, crude) as a white solid. MS (ESI) *m/z* 474.3 $[M+H]^+$

Step 6: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-fluoro-1H-indole-2-carboxamide

[00024] To a solution of N-[(1S)-1-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-fluoro-1H-indole-2-carboxamide (0.6 g, 1.27 mmol, 1 eq) in DCM (15 mL) was added Burgess reagent (452.92 mg, 1.90 mmol, 1.5 eq), and then the mixture was stirred at 40 °C for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40mm * 10um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 8 min) to give N-[(1S)-1-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-fluoro-1H-indole-2-carboxamide (230 mg, 495.32 umol, 39.09% yield, 98.1% purity) as a white solid. MS (ESI) *m/z* 456.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 12.03 (s, 1H), 8.97 (d, *J* = 7.7 Hz, 1H), 8.59 (d, *J* = 7.9 Hz, 1H), 7.54 (br s, 1H), 7.48 - 7.44 (m, 1H), 7.29 (d, *J* = 3.1 Hz, 1H), 7.07 - 6.97 (m, 2H), 5.09 - 5.01 (m, 1H), 4.59 - 4.51 (m, 1H), 3.11 - 3.02 (m, 2H), 2.30 - 2.18 (m, 2H), 1.87 - 1.77 (m, 2H), 1.76 - 1.64 (m, 3H), 1.59 - 1.48 (m, 1H), 1.44 - 1.34 (m, 1H), 0.94 (s, 9H).

Example 244. Synthesis of viral protease inhibitor compound 826



Step 1: methyl (Z)-2-azido-3-(2-chloro-5-fluoro-phenyl)prop-2-enoate

[00025] To a mixture of NaOMe (3.41 g, 63.07 mmol, 2 *eq*) in MeOH (30 mL) was cooled to -10 °C, a mixture of 2-chloro-5-fluoro-benzaldehyde (5 g, 31.53 mmol, 1 *eq*) and ethyl 2-azidoacetate (8.14 g, 63.07 mmol, 7.21 mL, 2 *eq*) in MeOH (100 mL) was drop-wise added, and then the mixture was stirred at 25 °C for 18 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue, the residue was diluted with H_2O 60 mL and extracted with EA 90 mL (30 mL * 3). The combined organic layers were washed with brine 45 mL (45 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0) to give methyl (Z)-2-azido-3-(2-chloro-5-fluoro-phenyl)prop-2-enoate (2.6 g, 10.17 mmol, 32.25% yield) as a yellow solid.

Step 2: methyl 4-chloro-7-fluoro-1H-indole-2-carboxylate

[00026] A mixture of methyl (Z)-2-azido-3-(2-chloro-5-fluoro-phenyl)prop-2-enoate (2.4 g, 9.39 mmol, 1 *eq*) in xylene (25 mL) was stirred at 170 °C for 1 h. Upon completion, the reaction mixture was filtered to give methyl 4-chloro-7-fluoro-1H-indole-2-carboxylate (700 mg, 3.08 mmol, 32.76% yield) as a white solid.

Step 3: 4-chloro-7-fluoro-1H-indole-2-carboxylic acid

[00027] A mixture of methyl 4-chloro-7-fluoro-1H-indole-2-carboxylate (700 mg, 3.08 mmol, 1 *eq*) in THF (4 mL) and H_2O (4 mL) was added $LiOH.H_2O$ (258.08 mg, 6.15 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 60 °C for 1 hour. Upon completion, the reaction mixture was adjusted to acidity by 1M HCl, extracted with EA 90 mL (30 mL * 3). The combined organic layers were washed with brine 45 mL (45 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-chloro-7-fluoro-1H-indole-2-carboxylic acid (600 mg, 2.81 mmol, 91.34% yield) as a white solid. (ESI) *m/z* 211.9 $[M-H]^+$

Step 4: methyl (2S)-2-[[(2S)-2-[(4-chloro-7-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[00028] To a mixture of 4-chloro-7-fluoro-1H-indole-2-carboxylic acid (500 mg, 2.34 mmol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (895.68 mg, 2.57 mmol, 1.1 *eq*, HCl) in DCM (10 mL) and DMF (3 mL) was added DMAP (857.96 mg, 7.02 mmol, 3 *eq*) and EDCI (897.50 mg, 4.68 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was diluted with H_2O 30 mL and extracted with EA 60 mL (20 mL * 3). The combined organic layers were washed with brine 30 mL (30 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 0/1) to give methyl (2S)-2-[[(2S)-2-[(4-chloro-7-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1 g, 1.97 mmol, 84.27% yield) as a white solid. MS (ESI) *m/z* 505.0 $[M-H]^+$

Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-7-fluoro-1H-indole-2-carboxamide

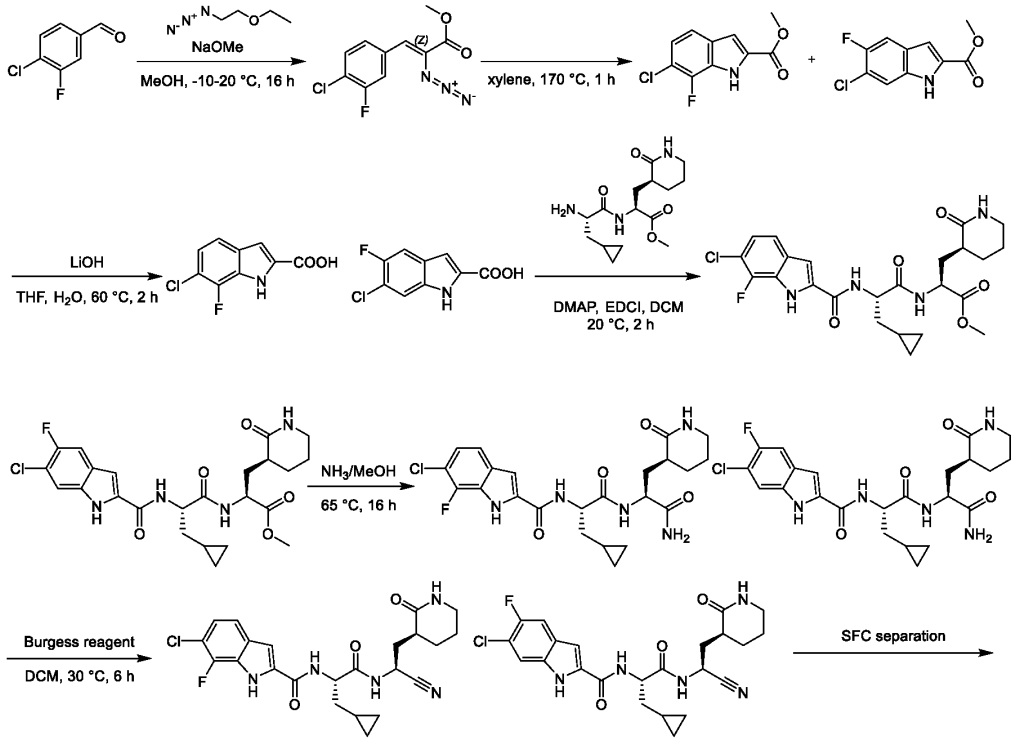
[00029] A mixture of methyl (2S)-2-[[(2S)-2-[(4-chloro-7-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.21 g, 2.17 mmol, 91% purity, 1 *eq*) in NH_3/MeOH (7 M, 20 mL, 64.52 *eq*) was stirred at 60 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-7-fluoro-

1H-indole-2-carboxamide (850 mg, 1.38 mmol, 63.70% yield, 80% purity) as a white solid. MS (ESI) *m/z* 492.2 $[M+H]^+$

Step 6: 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-fluoro-1H-indole-2-carboxamide

[00030] A mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-chloro-7-fluoro-1H-indole-2-carboxamide (780 mg, 1.27 mmol, 80% purity, 1 *eq*) in DCM (15 mL) was added Burgess reagent(604.57 mg, 2.54 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 40 °C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition;column: Waters Xbridge C18 150*50mm* 10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,10min) to give 4-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-fluoro-1H-indole-2-carboxamide (250 mg, 527.51 umol, 41.59% yield) as a white solid. MS (ESI) *m/z* 474.1 [M+H]. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.48 (br s, 1H), 8.96 (d, *J*=7.9 Hz, 1H), 8.79 (d, *J*=7.5 Hz, 1H), 7.54 (br s, 1H), 7.44 (d, *J*=2.6 Hz, 1H), 7.14 - 7.02 (m, 2H), 5.07 (q, *J*=7.8 Hz, 1H), 4.55 - 4.44 (m, 1H), 3.17 - 3.00 (m, 2H), 2.31 - 2.20 (m, 2H), 1.91 - 1.65 (m, 4H), 1.57 (br d, *J*=3.7 Hz, 1H), 1.52 - 1.34 (m, 2H), 0.89 - 0.75 (m, 1H), 0.49 - 0.35 (m, 2H), 0.26 - 0.05 (m, 2H)

Example 245. Synthesis of viral protease inhibitor compound 834 & 836



Step 1: ethyl (Z)-2-azido-3-(4-chloro-3-fluoro-phenyl)prop-2-enoate

[00031] To a solution of NaOMe (6.81 g, 126.14 mmol, 2 *eq*) in MeOH (70 mL) was added 4-chloro-3-fluoro-benzaldehyde (10 g, 63.07 mmol, 1 *eq*) and ethyl 2-azidoacetate (17.10 g, 132.44 mmol, 15.13 mL, 2.1 *eq*) in MeOH (100 mL) at -10 °C. Upon completion, the mixture was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove MeOH. The reaction mixture was quenched by addition H_2O 100 mL, and extracted with ethyl acetate 100 mL (50 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 10/1, Petroleum ether:Ethyl acetate = 5:1, (I2)) to give ethyl (Z)-2-azido-3-(4-chloro-3-fluoro-phenyl)prop-2-enoate (8.9 g, 29.70 mmol, 47.10% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 256.02 $[M+H]^+$

Step 2: methyl 6-chloro-7-fluoro-1H-indole-2-carboxylate and methyl 6-chloro-5-fluoro-1H-indole-2-carboxylate

[00032] To a solution of ethyl (Z)-2-azido-3-(4-chloro-3-fluoro-phenyl)prop-2-enoate (4 g, 14.83 mmol, 1 *eq*) in xylene (40 mL). The mixture was stirred at 170 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 5/1, Petroleum ether:Ethyl acetate = 5:1, (UV 254 nm)) to give mixture of methyl 6-chloro-7-fluoro-1H-indole-2-carboxylate (2.85 g, 5.61 mmol, 37.82% yield, 44.8% purity) and methyl 6-chloro-5-fluoro-1H-indole-2-carboxylate (2.85 g, 6.41 mmol, 43.22% yield, 51.2% purity) as a yellow solid. MS (ESI) *m/z* 228.01 $[M+H]^+$

Step 3: 6-chloro-7-fluoro-1H-indole-2-carboxylic acid and 6-chloro-5-fluoro-1H-indole-2-carboxylic acid

[00033] To a solution of methyl 6-chloro-7-fluoro-1H-indole-2-carboxylate (1 g, 1.97 mmol, 44.8% purity, 1 *eq*) and methyl 6-chloro-5-fluoro-1H-indole-2-carboxylate (1 g, 2.25 mmol, 51.2% purity, 1.14 *eq*) in THF (10 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (247.76 mg, 5.90 mmol, 3 *eq*). The mixture was stirred at 60 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove THF, then the reaction mixture was addition HCl (1 M) until pH = 3, and then extracted with EA 10 mL. The combined organic layers were washed with brine 10 mL, filtered and concentrated under reduced pressure to give 6-chloro-7-fluoro-1H-indole-2-carboxylic acid (680 mg, crude) and 6-chloro-5-fluoro-1H-indole-2-carboxylic acid (680 mg, crude) as a yellow solid. MS (ESI) *m/z* 214.00 $[M+H]^+$

Step 4: methyl (2S)-2-[[(2S)-2-[(6-chloro-7-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate and methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[00034] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.1 g, 3.16 mmol, 1 *eq*, HCl) and 6-chloro-7-fluoro-1H-indole-2-carboxylic acid (405.28 mg, 758.98 umol, 63.67 uL, 40% purity, 0.24 *eq*) and 6-chloro-5-fluoro-1H-indole-2-carboxylic acid (270.19 mg, 758.98 umol, 60% purity, 0.24 *eq*) in DCM (45 mL), then DMAP (1.16 g, 9.49 mmol, 3 *eq*) was added, and then EDCI (1.82 g, 9.49 mmol, 3 *eq*) was added.

The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 30 mL, and then extracted with DCM 40 mL (20 mL * 2). The combined organic layers were washed with HCl (1 M) 30 mL (15 mL * 2), the combined organic layers were washed with brine 30 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 to 0/1, Dichloromethane:Methanol = 10:1,(UV 254 nm)) to give methyl (2S)-2-[[(2S)-2-[(6-chloro-7-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (850 mg, 685.76 umol, 21.68% yield, 40.9% purity) and methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (850 mg, 989.24 umol, 31.28% yield, 59% purity) as a yellow solid. MS (ESI) *m/z* 507.17 $[M+H]^+$.

Step 5: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-7-fluoro-1H-indole-2-carboxamide and N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro-1H-indole-2-carboxamide

[00035] A solution of methyl (2S)-2-[[(2S)-2-[(6-chloro-7-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (830 mg, 669.63 umol, 40.9% purity, 1 *eq*) and methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (830.00 mg, 965.97 umol, 59% purity, 1.44 *eq*) in NH_3/MeOH (7 M, 4.08 mL, 42.68 *eq*) was stirred at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent and afford N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-7-fluoro-1H-indole-2-carboxamide (800 mg, crude) and N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro-1H-indole-2-carboxamide (800 mg, crude) as a yellow solid. MS (ESI) *m/z* 492.17 $[M+H]^+$.

Step 6: 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-fluoro-1H-indole-2-carboxamide and 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide

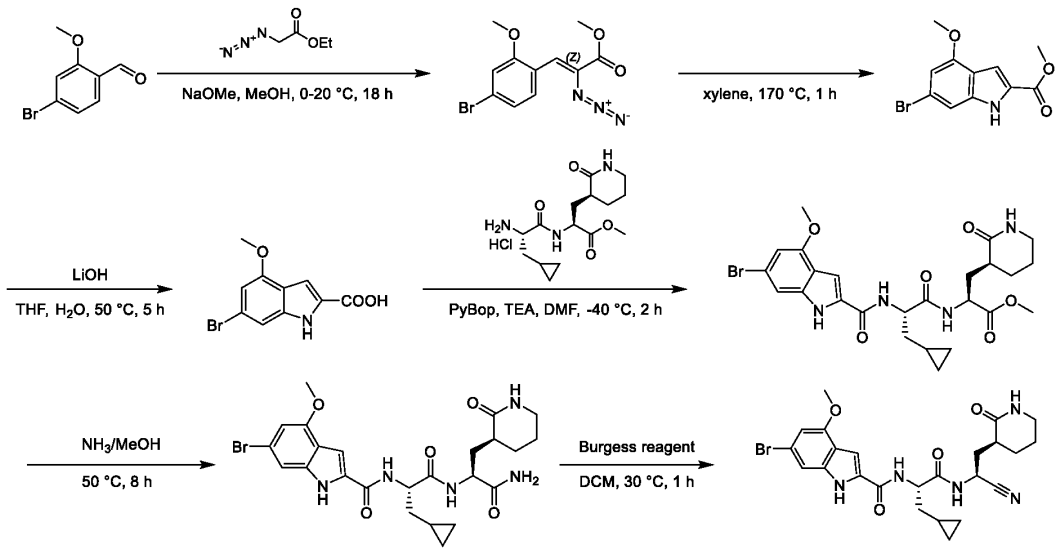
[00036] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-7-fluoro-1H-indole-2-carboxamide (780 mg, 635.81 umol, 40.1% purity, 1 *eq*) and N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro-1H-indole-2-carboxamide (780.00 mg, 948.16 umol, 59.8% purity, 1.49 *eq*) in DCM (18 mL) was added with Burgess reagent (303.04 mg, 1.27 mmol, 2 *eq*). The mixture was stirred at 30 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150*50mm* 10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 40%-65%,10min) to give 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-fluoro-1H-indole-2-carboxamide (500 mg, 422.01 umol, 66.37% yield, 40% purity) and 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide (500 mg, 633.01 umol, 99.56% yield, 60% purity) as a yellow solid. MS (ESI) *m/z* 474.16 $[M+H]^+$.

Step 7: 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-fluoro-1H-indole-2-carboxamide and 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide

[00037] 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide (500 mg) was separated by SFC column: DAICEL CHIRALCEL OD(250mm*30mm,10um);mobile phase: [0.1%NH3H2O MEOH];B%: 38%-38%,6min) to give 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-fluoro-1H-indole-2-carboxamide (109.43 mg, 230.21 umol, 54.55% yield, 99.7% purity) as a white solid. MS (ESI) *m/z* 474.16 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 0.04 - 0.29 (m, 2H), 0.30 - 0.52 (m, 2H), 0.71 - 0.90 (m, 1H), 1.32 -

1.63 (m, 3H), 1.65 - 1.90 (m, 4H), 2.16 - 2.37 (m, 2H), 2.97 - 3.18 (m, 2H), 4.41 - 4.55 (m, 1H), 4.97 - 5.13 (m, 1H), 7.13 (d, J = 8.56Hz, 1H), 7.34 (d, J = 3.06Hz, 1H), 7.43 - 7.58 (m, 2H), 8.65 (d, J = 7.46Hz, 1H), 8.97 (d, J = 7.95Hz, 1H), 12.31 (s, 1H)

Example 246. Synthesis of viral protease inhibitor compound 844



Step 1: (Z)-methyl 2-azido-3-(4-bromo-2-methoxyphenyl)acrylate

[00038] To a solution of NaOMe (1.00 g, 18.60 mmol, 2 *eq*) in MeOH (10 mL) was added 4-bromo-2-methoxy-benzaldehyde (2 g, 9.30 mmol, 1 *eq*) and ethyl 2-azidoacetate (2.40 g, 18.60 mmol, 2.13 mL, 2 *eq*) in MeOH (50 mL) at 0 °C. The mixture was stirred at 20 °C for 18 h. Upon the reaction completion, the mixture was concentration in vacuum, was added with water (150 mL) and then extracted with EtOAc (50 mL * 3). The resulting mixture was concentrated in vacuum and purified by column (SiO_2, PE:EA =1:0 to 10:1) to afford (*Z*)-methyl 2-azido-3-(4-bromo-2-methoxyphenyl)acrylate (1.6 g, 5.13 mmol, 55.12% yield) as a yellow solid.

Step 2: methyl 6-bromo-4-methoxy-1H-indole-2-carboxylate

[00039] A solution of (*Z*)-methyl 2-azido-3-(4-bromo-2-methoxyphenyl) acrylate (1.6 g, 5.13 mmol, 1 *eq*) in xylene (10 mL) the mixture was stirred at 170 °C for 1 h. Upon the reaction completion, the mixture was concentrated in vacuum and was trituration with petroleum ether (10 mL) and was filtered to obtained methyl 6-bromo-4-

methoxy-1*H*-indole-2-carboxylate (1.2 g, 4.22 mmol, 82.40% yield) as a white solid. MS (ESI) *m/z* 283.8 $[M+H]^+$

Step 3: 6-bromo-4-methoxy-1H-indole-2-carboxylic acid

[00040] A solution of methyl 6-bromo-4-methoxy-1*H*-indole-2-carboxylate (1.2 g, 4.22 mmol, 1 *eq*) in THF (12 mL) and H_2O (6 mL) was added $LiOH.H_2O$ (531.69 mg, 12.67 mmol, 3 *eq*), and then the mixture was stirred at 50 °C for 5 h. Upon the reaction completion, the mixture was concentrated in vacuum, was adjusted to pH~1 with 1M HCl (15 mL) and then extracted with EtOAc (5 mL * 3), then was concentrated in vacuum to obtained 6-bromo-4-methoxy-1*H*-indole-2-carboxylic acid (1 g, crude) as a white solid. MS (ESI) *m/z* 268.0 $[M-H]^+$

Step 4: (S)-methyl2-((S)-2-(6-bromo-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00041] To a solution of 6-bromo-4-methoxy-1*H*-indole-2-carboxylic acid (480 mg, 1.78 mmol, 1.2 *eq*) and methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl] propanoate (461.16 mg, 1.48 mmol, 1 *eq*) in DMF (20 mL) was added TEA (449.60 mg, 4.44 mmol, 618.43 uL, 3 *eq*) and PyBop (770.73 mg, 1.48 mmol, 1 *eq*) in DMF (1 mL), and then the mixture was stirred at -40 °C for 2 h. Upon the reaction completion, the mixture was quenched by water (30 mL) and was extracted with DCM (10 mL * 3), then concentrated in vacuum and purified by column (SiO_2, PE:EA = 1:1 to 0:1 to DCM:MeOH = 10:1) to afford (*S*)-methyl 2-((*S*)-2-(6-bromo-4-methoxy-1*H*-indole-2 -carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (800 mg, 993.90 umol, 67.11% yield, 70% purity) as a yellow gum. MS (ESI) *m/z* 563.2 $[M-H]^+$

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-bromo-4-methoxy-1H-indole-2-carboxamide

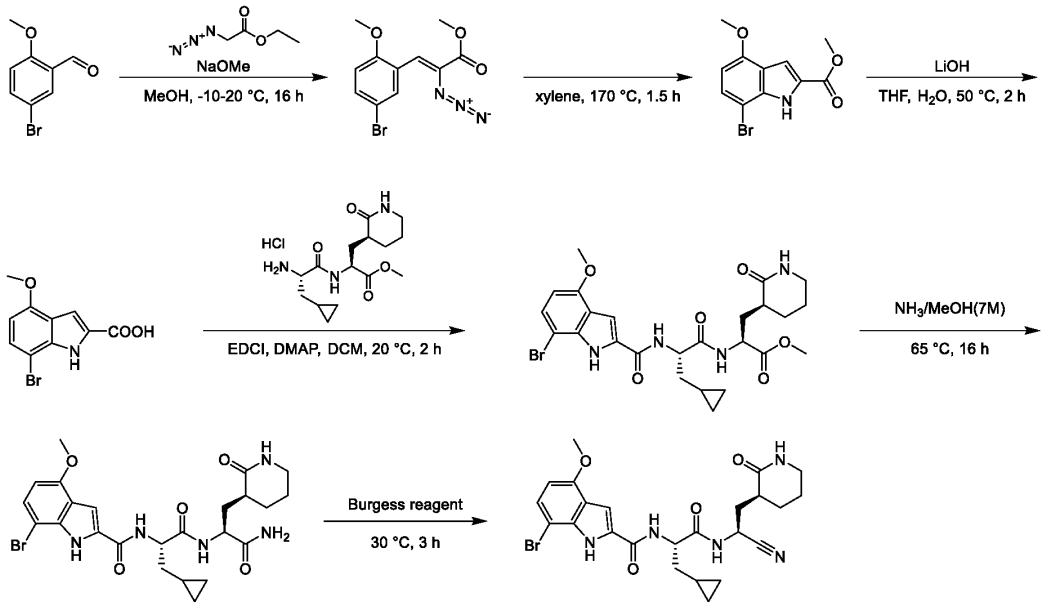
[00042] A solution of (*S*)-methyl 2-((*S*)-2-(6-bromo-4-methoxy-1*H*-indole-2 -carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl) propanoate (200 mg, 354.96 umol, 1 *eq*) in NH_3/MeOH (7M, 20 mL) was stirred at 50 °C for 8 h. Upon the reaction complteion, the mixture was concentrated in vacuum to obtained *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-

cyclopropyl-1-oxopropan-2-yl)-6-bromo-4-methoxy-1*H*-indole-2-carboxamide (600 mg, crude) as a white solid.

Step 6: 6-bromo-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[00043] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)- 3-cyclopropyl-1-oxopropan-2-yl)-6-bromo-4-methoxy-1*H*-indole-2-carboxamide (580 mg, 1.06 mmol, 1 *eq*) in DCM (8 mL) was added burgess reagent (756.07 mg, 3.17 mmol, 3 *eq*), and then the resulting mixture was stirred at 30 °C for 1 h. Upon the reaction completion, the mixture was quenched by water (1 mL) and was dried by blowing N_2 and was purified by prep-HPLC (column: Waters Xbridge C18 150 * 50mm * 10um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 30% - 60%, 10 min) to obtained 6-bromo-*N*-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide (130 mg, 227.94 umol, 21.55% yield, 93% purity) as a white solid. MS (ESI) *m/z* 530.0 $[M+H]^+$. ^1H NMR (400MHz, DMSO-d_6) δ ppm 11.72 (d, *J* = 1.9 Hz, 1H), 8.90 (d, *J* = 8.1 Hz, 1H), 8.57 (d, *J* = 7.5 Hz, 1H), 7.52 (s, 1H), 7.38 (d, *J* = 1.5 Hz, 1H), 7.19 (s, 1H), 6.66 (d, *J* = 1.3 Hz, 1H), 5.06 (q, *J* = 8.1 Hz, 1H), 4.49 - 4.39 (m, 1H), 3.91 (s, 3H), 3.14 - 3.02 (m, 2H), 2.30 - 2.21 (m, 2H), 1.88 - 1.75 (m, 3H), 1.74 - 1.66 (m, 1H), 1.62 - 1.51 (m, 1H), 1.49 - 1.32 (m, 2H), 0.86 - 0.74 (m, 1H), 0.46 - 0.35 (m, 2H), 0.24 - 0.05 (m, 2H).

Example 247. Synthesis of viral protease inhibitor compound 846



Step 1: (Z)-methyl 2-azido-3-(5-bromo-2-methoxyphenyl)acrylate

[00044] To a solution of NaOMe (2.51 g, 46.50 mmol, 2 *eq*) in MeOH (25 mL) was added 5-bromo-2-methoxy-benzaldehyde (5 g, 23.25 mmol, 1 *eq*) and ethyl 2-azidoacetate (6.30 g, 48.83 mmol, 5.58 mL, 2.1 *eq*) in MeOH (25 mL) at -10 °C. The mixture was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O 100 mL and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with solvent brine (100 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give methyl (Z)-2-azido-3-(5-bromo-2-methoxy-phenyl)prop-2-enoate (2.1 g, crude) as a yellow solid.

Step 2: methyl 7-bromo-4-methoxy-1H-indole-2-carboxylate

[00045] A solution of methyl (Z)-2-azido-3-(5-bromo-2-methoxy-phenyl)prop-2-enoate (2.1 g, 6.73 mmol, 1 *eq*) in XYLENE (43 mL) was stirred at 170 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give methyl 7-bromo-4-methoxy-1H-indole-2-carboxylate (100 mg, crude) as a yellow solid.

Step 3: 7-bromo-4-methoxy-1H-indole-2-carboxylic acid

[00046] To a solution of methyl 7-bromo-4-methoxy-1H-indole-2-carboxylate (100 mg, 351.98 umol, 1 *eq*) in THF (7 mL) and H_2O (3.5 mL) was added $LiOH.H_2O$ (44.31 mg, 1.06 mmol, 3 *eq*). The mixture was stirred at 50 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. 1M HCl was added, adjust pH to 3, then was filtered and concentrated under reduced pressure to give 7-bromo-4-methoxy-1H-indole-2-carboxylic acid (50 mg, crude) as a yellow solid.

Step 4: (S)-methyl 2-((S)-2-(7-bromo-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00047] To a solution of 7-bromo-4-methoxy-1H-indole-2-carboxylic acid (500 mg, 1.85 mmol, 1 *eq*), methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (772.74 mg, 2.22 mmol, 1.2 *eq*, HCl), DMAP (678.51 mg, 5.55 mmol, 3 *eq*) in DCM (10 mL) was added EDCI (709.80 mg, 3.70 mmol, 2 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O 30 mL at 20 °C, and then extracted with DCM (35 mL * 3). The combined organic layers were washed with brine (35 mL *2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 10/1) to give methyl (2S)-2-[[(2S)-2-[(7-bromo-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (460 mg, 816.41 umol, 44.10% yield) as a yellow solid.

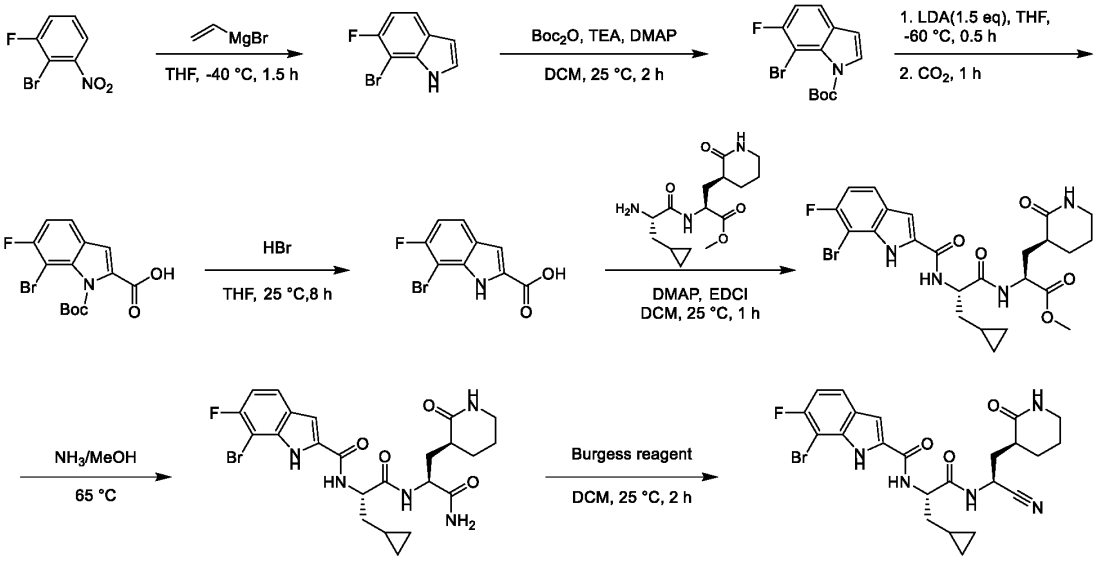
Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-bromo-4-methoxy-1H-indole-2-carboxamide

[00048] To a solution of methyl (2S)-2-[[(2S)-2-[(7-bromo-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (450 mg, 798.67 umol, 1 *eq*) in NH_3/MeOH (7 M, 18 mL, 157.76 *eq*). The mixture was stirred at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove MeOH to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-bromo-4-methoxy-1H-indole-2-carboxamide (430 mg, crude) as a yellow solid. MS (ESI) *m/z* 548.1 $[M+H]^+$.

Step 6: 7-bromo-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[00049] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-bromo-4-methoxy-1H-indole-2-carboxamide (420 mg, 765.82 umol, 1 *eq*) in DCM (5 mL) was added Burgess reagent (365.00 mg, 1.53 mmol, 2 *eq*). The mixture was stirred at 30 °C for 3 h. Upon completion, the reaction mixture was poured into H_2O 20 mL at 20 °C, and then extracted with DCM (25 mL * 3). The combined organic layers were washed with brine (20mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um;mobile phase: [water(0.2%FA)-ACN];B%: 30%-70%,8min) to give 7-bromo-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (95.7 mg, 180.43 umol, 23.56% yield, 100% purity) as a white solid. MS (ESI) *m/z* 530.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.46 (d, *J* = 1.5Hz, 1H), 8.98 (d, *J* = 7.9Hz, 1H), 8.72 (d, *J* = 7.6Hz, 1H), 7.52 (s, 1H), 7.35 (d, *J* = 8.2Hz, 1H), 7.28 (d, *J* = 2.1Hz, 1H), 6.54 (d, *J* = 8.3Hz, 1H), 5.07 (d, *J* = 7.9Hz, 1H), 4.51 (d, *J* = 6.2Hz, 1H), 3.89 (s, 3H), 3.17 - 3.00 (m, 2H), 2.26 (t, *J* = 8.7Hz, 2H), 1.81 (dd, *J* = 8.5, 14.2Hz, 4H), 1.49 (s, 3H), 0.89 - 0.73 (m, 1H), 0.52 - 0.36 (m, 2H), 0.25 - 0.04 (m, 2H).

Example 248. Synthesis of viral protease inhibitor compound 850



Step 1: 7-bromo-6-fluoro-1H-indole

[00050] To a solution of 2-bromo-1-fluoro-3-nitro-benzene (8 g, 36.36 mmol, 1 *eq*) in THF (110 mL) was added bromo (vinyl) magnesium (1 M, 127.28 mL, 3.5 *eq*) drop-wise at -40 °C under N_2. The reaction mixture was stirred at -40 °C for another 1.5 hr. Upon completion, the residue was poured into NH_4Cl *aq* (200 mL) under N_2 and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (200 mL * 4). The combined organic phase was washed with brine (300 mL * 2), dried with anhydrous Na_2SO4, filtered andconcentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 10/1) to give 7-bromo-6-fluoro-1H-indole (2.4 g, 11.21 mmol, 30.84% yield, N/A purity) was obtained as a yellow oil. MS (ESI) *m/z* 213.0 $[M+H]^+$.

Step 2: tert-butyl 7-bromo-6-fluoro-1H-indole-1-carboxylate

[00051] To a solution of 7-bromo-6-fluoro-1H-indole (2.4 g, 11.21 mmol, 1 *eq)* and TEA (1.36 g, 13.46 mmol, 1.87 mL, 1.2 *eq*) in DCM (25 mL) was added Boc_2O (2.69 g, 12.33 mmol, 2.83 mL, 1.1 *eq*) and DMAP (273.98 mg, 2.24 mmol, 0.2 *eq*). The mixture was stirred at 25 °C for 2 hr. Upon completion, the reaction mixture was quenched by addition H_2O 40 mL, and extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 10/1) to give

tert-butyl 7-bromo-6-fluoro-indole-1-carboxylate (3 g, 8.88 mmol, 79.20% yield, 93% purity) was obtained as a yellow oil. MS (ESI) *m/z* 313.0 $[M+H]^+$.

Step 3: 7-bromo-1-(tert-butoxycarbonyl)-6-fluoro-1H-indole-2-carboxylic acid

[00052] To a solution of tert-butyl 7-bromo-6-fluoro-indole-1-carboxylate (3 g, 9.55 mmol, 1 *eq)* in THF (30 mL) was added LDA (2 M, 5.25 mL, 1.1 *eq*) drop-wise at -60 °C under N_2. The reaction mixture was stirred at -60 °C for 0.5 h, then the above solution was added into drikold (21.01 g, 1.00 *eq*). The reaction mixture was stirred at 25 °C for another 1 hrs. Upon completion, the reaction mixture was poured into H_2O (80 mL) under N_2 and stirred for 10 min. The aqueous phase was added with 1M HCl to adjust pH~2 at 0 °C and extracted with ethyl acetate (40 mL * 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 15 um); mobile phase: [water (0.2%FA)-ACN]; B%: 40%-70%, 20 min) to give 7-bromo-1-tert-butoxycarbonyl-6-fluoro-indole-2-carboxylic acid (900 mg, 2.51 mmol, 26.31% yield, N/A purity) was obtained as a white solid.MS (ESI) *m/z* 357.0 $[M+H]^+$.

Step 4: 7-bromo-6-fluoro-1H-indole-2-carboxylic acid

[00053] To a solution of 7-bromo-1-tert-butoxycarbonyl-6-fluoro-indole-2-carboxylic acid (900 mg, 2.51 mmol, 1 *eq*) in THF (10 mL) and was added HBr (14.90 g, 73.66 mmol, 10 mL, 40% purity, 29.31 *eq*). The mixture was stirred at 25 °C for 8 hr. Upon completion, the reaction mixture was quenched by addition H_2O (40 mL) and extracted with EtOAc (25 mL * 4). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound 7-bromo-6-fluoro-1H-indole-2-carboxylic acid (650 mg, crude) was obtained as a yellow solid. MS (ESI) *m/z* 256.9 $[M+H]^+$.

Step 5: (S)-methyl 2-((S)-2-(7-bromo-6-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00054] To a solution of 7-bromo-6-fluoro-1H-indole-2-carboxylic acid (650 mg, 2.52 mmol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (876.18 mg, 2.52 mmol, 1 *eq*, HCl) in DCM (25 mL) was added DMAP (615.47 mg, 5.04 mmol, 2 *eq*) and EDCI (724.33 mg, 3.78

mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction was quenched by H_2O 60 mL slowly and then extracted with DCM (30mL * 3). The combined organic phase was washed with brine (45 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 to 0/1) to afford methyl (2S)-2-[[(2S)-2-[(7-bromo-6-fluoro-1H-indole-2-carbonyl) amino]-3-cyclopropyl-propanoyl] amino]-3-[(3S)-2-oxo-3-piperidyl] propanoate (0.75 g, 1.29 mmol, 51.30% yield, 95% purity) was obtained as a yellow solid. MS (ESI) *m/z* 550.1 $[M+H]^+$.

Step 6: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-bromo-6-fluoro-1H-indole-2-carboxamide

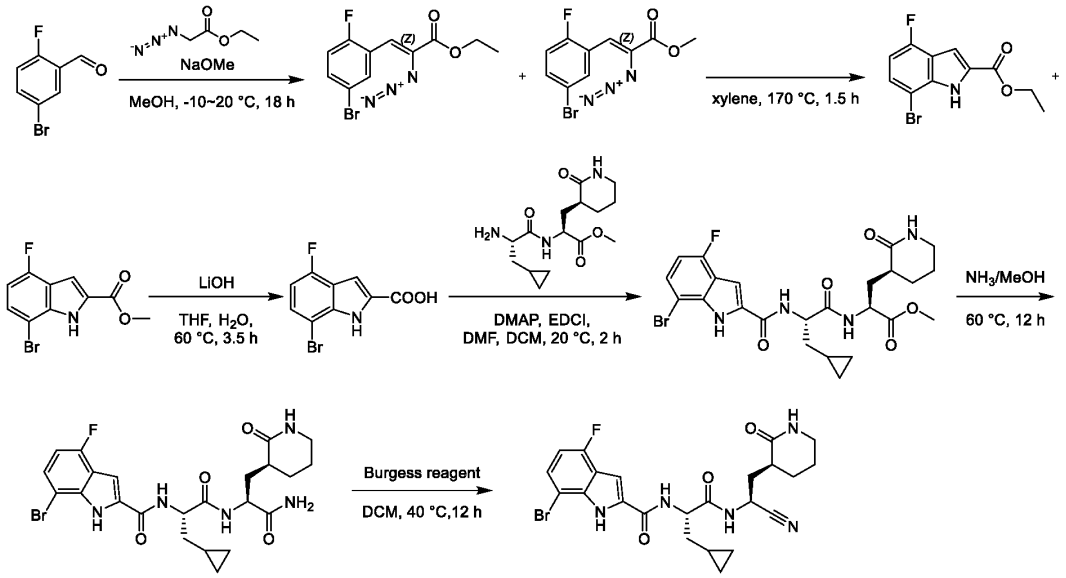
[00055] A solution of methyl (2S)-2-[[(2S)-2-[(7-bromo-6-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (800 mg, 1.45 mmol, 1 *eq*) in NH_3MeOH (7 M, 40 mL, 192.99 *eq*) was stirred at 65 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove DCM to give N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-bromo-6-fluoro-1H-indole-2-carboxamide (730 mg, crude) was obtained as a brown solid. MS (ESI) *m/z* 535.1 $[M+H]^+$.

Step 7: 7-bromo-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-fluoro-1H-indole-2-carboxamide

[00056] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-bromo-6-fluoro-1H-indole-2-carboxamide (730 mg, 1.36 mmol, 1 *eq*) in DCM (15 mL) was added Burgess reagent (648.64 mg, 2.72 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under N_2 at 25 °C. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 40%-55%, 8min) to give 7-bromo-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-fluoro-1H-indole-2-carboxamide (235 mg, 453.34 umol, 33.31% yield, 100% purity) was

obtained as a white solid. MS (ESI) *m/z* 517.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ = 11.72 - 11.49 (m, 1H), 9.11 - 8.90 (m, 1H), 8.55 - 8.37 (m, 1H), 7.67 - 7.49 (m, 2H), 7.06 - 6.93 (m, 1H), 6.68 - 6.60 (m, 1H), 5.17 - 5.04 (m, 1H), 4.65 - 4.55 (m, 1H), 3.17 - 3.00 (m, 2H), 2.37 - 2.19 (m, 2H), 1.94 - 1.66 (m, 4H), 1.62 - 1.32 (m, 3H), 0.84 - 0.72 (m, 1H), 0.52 - 0.37 (m, 2H), 0.21 - 0.05 (m, 2H).

Example 249. Synthesis of viral protease inhibitor compound 854



Step 1: (Z)-ethyl 2-azido-3-(5-bromo-2-fluorophenyl)acrylate and (Z)-methyl 2-azido-3-(5-bromo-2-fluorophenyl)acrylate

[00057] A mixture of NaOMe (2.66 g, 49.26 mmol, 2 eq) in MeOH (30 mL) was cooled to -10 °C, and then a mixture of 5-bromo-2-fluoro-benzaldehyde (5 g, 24.63 mmol, 1 eq) and ethyl 2-azidoacetate (6.36 g, 49.26 mmol, 5.63 mL, 2 eq) in MeOH (70 mL) was added drop-wise to the former solution. The mixture was stirred at 20 °C for 18 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove MeOH 60 mL. The residue was diluted with H_2O 100 mL and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 100:1) to get the product ethyl (Z)-2-azido-3-(5-bromo-2-fluoro-phenyl)prop-2-enoate (1.6 g, 5.09 mmol, 20.68% yield) as a yellow solid and methyl

(Z)-2-azido-3-(5-bromo-2-fluoro-phenyl)prop-2-enoate (1.6 g, 5.33 mmol, 21.65% yield) as a yellow solid .

Step 2: ethyl 7-bromo-4-fluoro-1H-indole-2-carboxylate and methyl 7-bromo-4-fluoro-1H-indole-2-carboxylate

[00058] A mixture of ethyl (Z)-2-azido-3-(5-bromo-2-fluoro-phenyl)prop-2-enoate (1.6 g, 5.09 mmol, 1 eq) and methyl (Z)-2-azido-3-(5-bromo-2-fluoro-phenyl)prop-2-enoate (1.6 g, 5.33 mmol, 1.05 eq) in xylene (30 mL) was stirred at 170 °C for 1.5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 100:1) to afford ethyl 7-bromo-4-fluoro-1H-indole-2-carboxylate (0.35 g, 1.22 mmol, 24.02% yield) as a white solid and methyl 7-bromo-4-fluoro-1H-indole-2-carboxylate (0.35 g, 1.29 mmol, 25.26% yield) as a white solid.

Step 3: 7-bromo-4-fluoro-1H-indole-2-carboxylic acid

[00059] To a solution of ethyl 7-bromo-4-fluoro-1H-indole-2-carboxylate (250 mg, 873.83 umol, 1 eq) in THF (6 mL) and H_2O (3 mL) was added $LiOH.H_2O$ (110.00 mg, 2.62 mmol, 3 eq), and then the mixture was stirred at 60 °C for 3.5 h. Upon completion, the reaction mixture was quenched by addition H_2O 60 mL at 0 °C, 1M HCl was added drop-wise to adjust the pH to about 5, and then extracted with EtOAc (40 mL * 3). The combined organic layers were washed with brine 30 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get the product 7-bromo-4-fluoro-1H-indole-2-carboxylic acid (200 mg, crude) was obtained as a white solid. MS (ESI) *m/z* 255.9 $[M-H]^+$.

[00060] To a solution of methyl 7-bromo-4-fluoro-1H-indole-2-carboxylate (350 mg, 1.29 mmol, 1 eq) in THF (6 mL) and H_2O (3 mL), then $LiOH.H_2O$ (161.94 mg, 3.86 mmol, 3 eq) was added, the mixture was stirred at 60 °C for 3.5 h. Upon completion, the reaction mixture was quenched by addition H_2O 60 mL at 0 °C and added drop-wise 1M HCl to pH = 5, and then extracted with EtOAc (40 mL * 3). The combined organic layers were washed with brine 30 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get the product 7-bromo-4-fluoro-1H-indole-2-carboxylic acid (300 mg, crude) was obtained as a white solid.

Step 4: (S)-methyl 2-((S)-2-(7-bromo-4-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00061] To a solution of 7-bromo-4-fluoro-1H-indole-2-carboxylic acid (500 mg, 1.94 mmol, 1 eq) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (876.18 mg, 2.52 mmol, 1.30 eq, HCl) in DCM (10 mL), then DMAP (710.16 mg, 5.81 mmol, 3 eq) and EDCI (742.91 mg, 3.88 mmol, 2 eq) was added, the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 60 mL at 0 °C, and then extracted with DCM (40 mL * 3). The combined organic layers were washed with brine 60 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 0:1) to get the product methyl (2S)-2-[[(2S)-2-[(7-bromo-4-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (600 mg, 1.09 mmol, 56.16% yield) as a white solid. MS (ESI) *m/z* 551.1 $[M+H]^+$

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-bromo-4-fluoro-1H-indole-2-carboxamide

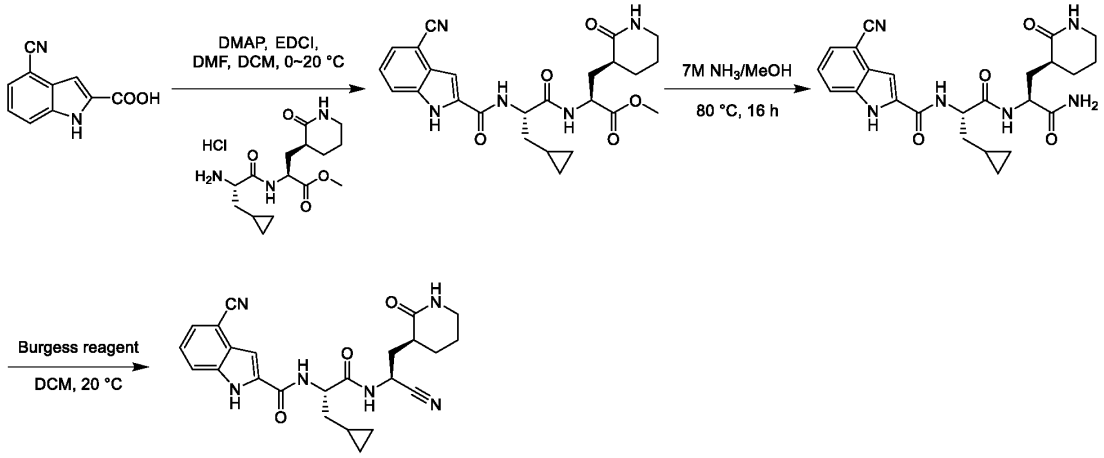
[00062] A solution of methyl (2S)-2-[[(2S)-2-[(7-bromo-4-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.6 g, 1.09 mmol, 1 eq) in NH_3/MeOH (7 M, 30.00 mL, 192.99 eq) was stirred at 60 °C for 12 h. The reaction mixture was concentrated under reduced pressure to get the product N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-bromo-4-fluoro-1H-indole-2-carboxamide (550 mg, crude) was obtained as a white solid. MS (ESI) *m/z* 536.1 $[M+H]^+$.

Step 6: 7-bromo-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-fluoro-1H-indole-2-carboxamide

[00063] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-bromo-4-fluoro-1H-indole-2-carboxamide (550 mg, 1.03 mmol, 1 eq) in DCM (20 mL) was added burgess reagent (488.70 mg, 2.05 mmol, 2 eq), and then the mixture was stirred

at 40 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 8 min) to ge the product 7-bromo-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-fluoro-1H-indole-2-carboxamide (230 mg, 443.69 umol, 43.27% yield, 100% purity) was obtained as a white solid. MS (ESI) *m/z* 518.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.76 (br s, 1H), 9.01 (d, *J* = 7.9 Hz, 1H), 8.84 (d, *J* = 7.5 Hz, 1H), 7.53 (br s, 1H), 7.48 - 7.40 (m, 1H), 7.34 (s, 1H), 6.94 - 6.79 (m, 1H), 5.15 - 5.02 (m, 1H), 4.60 - 4.46 (m, 1H), 3.17 - 3.00 (m, 2H), 2.31 - 2.17 (m, 2H), 1.90 - 1.66 (m, 4H), 1.63 - 1.35 (m, 3H), 0.91 - 0.75 (m, 1H), 0.53 - 0.38 (m, 2H), 0.24 - 0.17 (m, 1H), 0.15 - 0.07 (m, 1H).

Example 250. Synthesis of viral protease inhibitor compound 858



Step 1: (S)-methyl 2-((S)-2-(4-cyano-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00064] To a mixture of (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1.05 g, 2.40 mmol, 80% purity, 1.1 *eq*, HCl) in DCM (4 mL) and DMF (1 mL) was added 4-cyano-1H-indole-2-carboxylic acid (500 mg, 2.69 mmol, 1 *eq*). After the addition of EDCI (1.03 g, 5.37 mmol, 2 *eq*) and DMAP (984.36 mg, 8.06 mmol, 3 *eq*) at 0 °C, the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by the addition of water (3 mL), and

then extracted with DCM (3 mL * 2). The combined organic layers were washed with HCl (1M, 3 mL), then washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, DCM:MeOH = 100:1 to 10:1) to give (S)-methyl 2-((S)-2-(4-cyano-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (750 mg, 1.49 mmol, 55.32% yield, 95% purity) as yellow solid. MS (ESI) *m/z* 480.1 $[M+H]^+$.

Step 2: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-cyano-1H-indole-2-carboxamide

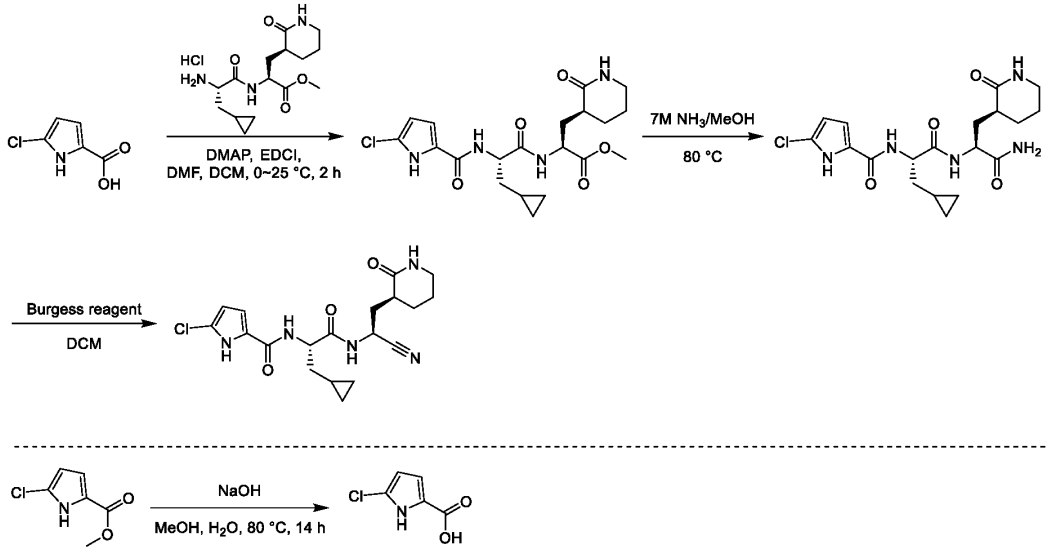
[00065] A mixture of (S)-methyl 2-((S)-2-(4-cyano-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (700 mg, 1 *eq*) in NH_3/MeOH (7 M, 5 mL, 745.93 *eq*) was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-cyano-1H-indole-2-carboxamide (670 mg, crude) as yellow solid. MS (ESI) *m/z* 465.2 $[M+H]^+$.

Step 3: 4-cyano-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-indole-2-carboxamide

[00066] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-cyano-1H-indole-2-carboxamide (670 mg, 1.37 mmol, 95% purity, 1 *eq*) in DCM (10 mL) was added burgess reagent (979.63 mg, 4.11 mmol, 3 *eq*) and stirred at 20 °C for 14 h. Upon completion, the mixture was quenched with water (1 mL) and concentrated under reduced pressure to give a residue (<30 °C). The residue was purified by prep-HPLC (column: Waters Xbridge C18 150* 50 mm* 10 um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-55%, 10 min) to give 4-cyano-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-indole-2-carboxamide (40.4 mg, 90.48 umol, 6.60% yield, 100% purity) as off-white solid. MS (ESI) *m/z* 447.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.84 - 7.68 (m, 1H), 7.60 - 7.46 (m, 1H), 7.46 - 7.39 (m, 1H), 7.39 - 7.29 (m, 1H), 5.18 - 5.01 (m,

1H), 4.66 - 4.48 (m, 1H), 3.29 - 3.15 (m, 2H), 2.57 - 2.27 (m, 2H), 2.05 - 1.46 (m, 7H), 1.01 - 0.73 (m, 1H), 0.61 - 0.45 (m, 2H), 0.28 - 0.11 (m, 2H)

Example 245. Synthesis of viral protease inhibitor compound 864



Step 1: 5-chloro-1H-pyrrole-2-carboxylic acid

[00067] To a mixture of methyl 5-chloro-1H-pyrrole-2-carboxylate (500 mg, 3.13 mmol, 1 *eq*) in MeOH (2 mL) was added a solution of NaOH (250.66 mg, 6.27 mmol, 2 *eq*) in H_2O (2 mL) and then the resulting mixture was stirred at 80 °C for 14 h. Upon completion, the mixture was concentrated under reduced pressure to give 5-chloro-1H-pyrrole-2-carboxylic acid (500 mg, crude) as yellow oil. MS (ESI) *m/z* 146.0 $[M+H]^+$.

Step 2: (S)-methyl 2-((S)-2-(5-chloro-1H-pyrrole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[00068] To a mixture of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.49 g, 3.44 mmol, 80% purity, 1 *eq*, HCl) in DMF (1 mL) and DCM (4 mL) was added 5-chloro-1H-pyrrole-2-carboxylic acid (500 mg, 3.44 mmol, 1 *eq*), and then DMAP (1.26 g, 10.31 mmol, 3 *eq*) and EDCI (1.32 g, 6.87 mmol, 2 *eq)* were added at 0 °C, then the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched by the addition ofo water (10 mL), and then extracted with DCM (10 mL * 3). The combined organic

layers were washed with HCl (1M, 10 mL), then washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 100:1 to 10:1) to give (S)-methyl 2-((S)-2-(5-chloro-1H-pyrrole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (300 mg, 683.52 umol, 19.90% yield) as yellow solid. MS (ESI) *m/z* 439.1 $[M+H]^+$.

Step 3: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-chloro-1H-pyrrole-2-carboxamide

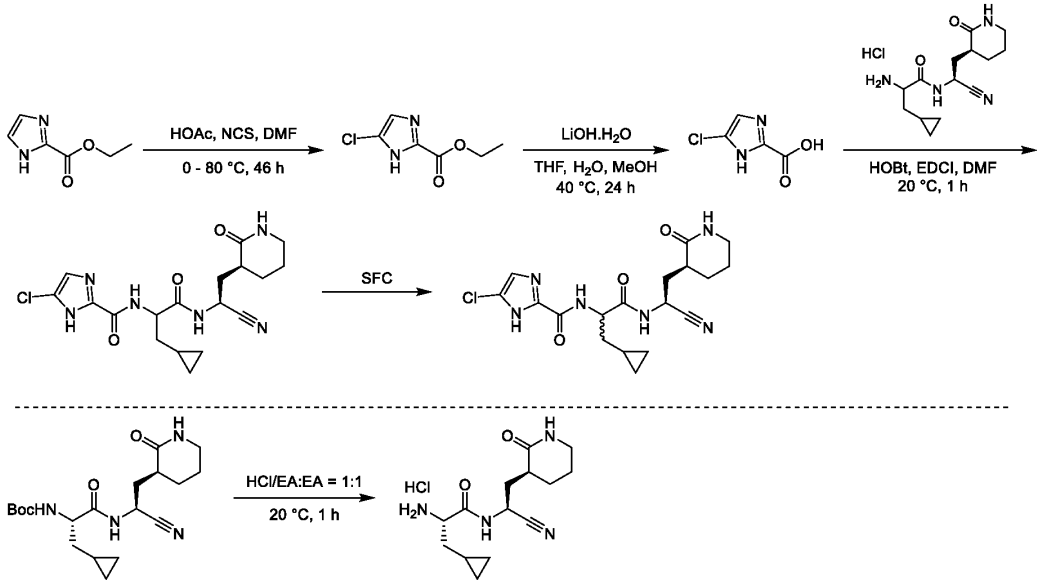
[00069] A mixture of methyl (2S)-2-[[(2S)-2-[(5-chloro-1H-pyrrole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (300 mg, 683.52 umol, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 102.41 *eq*) was stirred at 80 °C for 30 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-chloro-1H-pyrrole-2-carboxamide (280 mg, crude) as yellow solid. MS (ESI) *m/z* 424.1 $[M+H]^+$.

Step 4: 5-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrole-2-carboxamide

[00070] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-chloro-1H-pyrrole-2-carboxamide (220 mg, 467.10 umol, 90% purity, 1 *eq*) in DCM (3 mL) was added burgess reagent (333.94 mg, 1.40 mmol, 3 *eq*) and then the resulting mixture was stirred at 25 °C for 4 h. Upon completion, the mixture was quenched with water (1 mL) and concentrated under reduced pressure to give a residue (<30 °C). The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150* 40 mm* 10 um; mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 20%-50%, 8 min) to give 5-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrole-2-carboxamide (30.49 mg, 75.12 umol, 16.08% yield, 100% purity) as white solid. MS (ESI) *m/z* 406.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.36 (s, 1H), 9.10 - 8.81 (m, 1H), 8.13 - 8.03 (m, 1H), 7.52 (br s, 1H), 6.96 - 6.50 (m, 1H), 6.45 - 6.02 (m, 1H), 5.17 - 4.88 (m, 1H), 4.49 - 4.31 (m, 1H), 3.15 - 3.01 (m, 2H), 2.29 - 2.14 (m, 2H), 1.88 - 1.66 (m, 4H), 1.61 -

1.48 (m, 1H), 1.47 - 1.25 (m, 2H), 0.84 - 0.63 (m, 1H), 0.53 - 0.24 (m, 2H), 0.20 - 0.01 (m, 2H)

Example 251. Synthesis of viral protease inhibitor compound 868



Step 1: ethyl 5-chloro-1H-imidazole-2-carboxylate

[00071] To a solution of ethyl 1H-imidazole-2-carboxylate (5 g, 35.68 mmol, 1 *eq*) in DMF (150 mL) was added acetic acid (1 mL) dropwise, and then NCS (3.00 g, 22.47 mmol, 0.63 *eq*) in DMF (30 mL) was added at 0 °C, the mixture was stirred at 20 °C for 20 h, and then at 45 °C for 24 h, and then at 80 °C for 2 h. Upon completion, the reaction mixture was diluted with water (100 mL) and extracted with EA (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 1:0 to 65:35) to get product ethyl 5-chloro-1H-imidazole-2-carboxylate (2 g, 8.02 mmol, 22.48% yield, 70% purity) as light yellow solid. MS (ESI) m/z 175.1 $[M+H]^+$.

Step 2: 5-chloro-1H-imidazole-2-carboxylic acid

[00072] To a mixture of ethyl 5-chloro-1H-imidazole-2-carboxylate (2.5 g, 10.02 mmol, 70% purity, 1 *eq*) in THF (30 mL) and H_2O (10 mL) and MeOH (3 mL) was added $LiOH.H_2O$ (1.05 g, 25.06 mmol, 2.5 *eq*). The mixture was stirred at 40 °C for 24 h. Upon completion, the reaction mixture was concentrated under reduced pressure to

give a residue. The residue was purified by prep-HPLC (TFA column: Waters X bridge C18 150 * 50 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 1% - 15%, 10 min) to get the product 5-chloro-1H-imidazole-2-carboxylic acid (1.0 g, 6.82 mmol, 68.08% yield) as white solid. MS (ESI) m/z 145.1 $[M+H]^+$.

Step 3: (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-cyclopropyl-propanamide

[00073] A mixture of tert-butyl N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (2.1 g, 5.55 mmol, 1 *eq*) in EA (12 mL) was added HCl/EA (4 M, 12 mL, 8.65 *eq*). The mixture was stirred 20 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with ethyl acetate (20 mL * 3) and concentrated under reduced pressure to get the product (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-cyclopropyl-propanamide (1.7 g, crude, HCl) as white solid. MS (ESI) m/z 279.1 $[M+H]^+$.

Step 4: 5-chloro-N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide

[00074] To a solution of 5-chloro-1H-imidazole-2-carboxylic acid (800 mg, 5.46 mmol, 2.02 *eq*) in DMF (20 mL) was added HOBt (729.67 mg, 5.40 mmol, 2 *eq*), EDCI (1.04 g, 5.40 mmol, 2 *eq*) and (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-cyclopropyl-propanamide (1.7 g, 2.70 mmol, 50% purity, 1 *eq*, HCl). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with EA (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge C18 150 * 50 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 15% - 45%, 10 min) to get the product 5-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (500 mg, 1.23 mmol, 45.51% yield) as white solid. MS (ESI) m/z 407.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.59 (br s, 1H), 8.96 - 8.79 (m, 1H), 8.42 - 8.28 (m, 1H), 7.52 (br s, 1H), 7.40 (s, 1H), 5.11 - 4.88 (m, 1H),

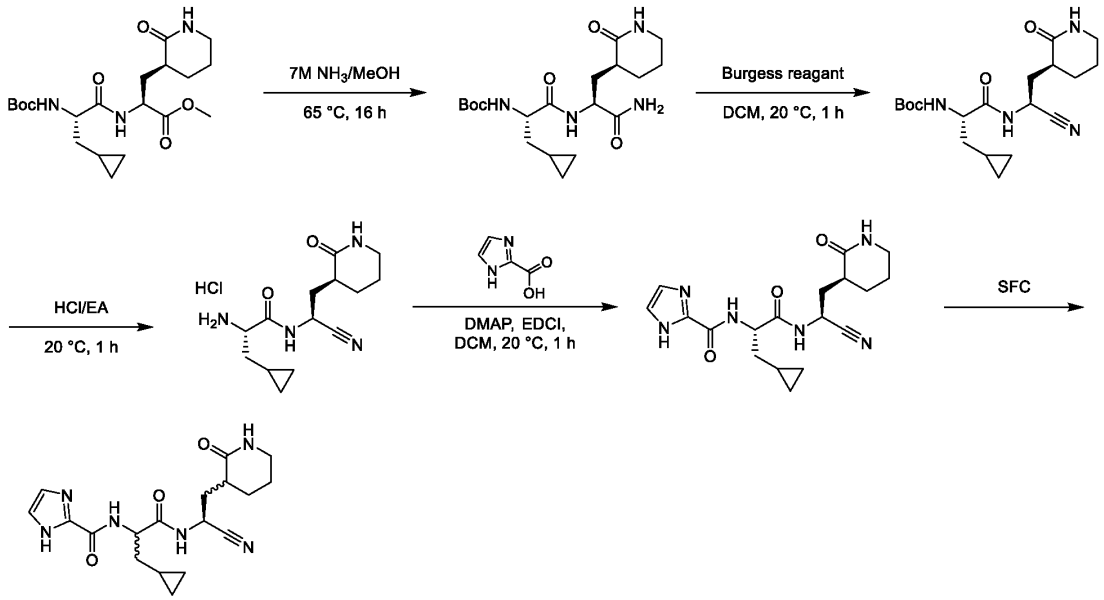
4.53 - 4.35 (m, 1H), 3.07 (br s, 2H), 2.32 - 2.10 (m, 2H), 1.81 (br s, 4H), 1.62 - 1.34 (m, 3H), 0.78 - 0.63 (m, 1H), 0.39 (br d, J = 7.8 Hz, 2H), 0.21 - 0.05 (m, 2H).

[00075] 5-chloro-N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (300 mg, 737.34 umol, 1 *eq*) was separated by SFC (column: DAICEL CHIRALPAK IF (250 mm * 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 27% - 27%, 9 min) to afford 5-chloro-N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide Isomer 1 (197.02 mg, 484.24 umol, 65.67% yield) as white solid. MS (ESI) m/z 407.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 13.47 (br s, 1H), 8.85 (br d, J = 8.0 Hz, 1H), 8.40 (br d, J = 8.0 Hz, 1H), 7.52 (br s, 1H), 7.43 (s, 1H), 5.17 - 4.92 (m, 1H), 4.54 - 4.25 (m, 1H), 3.09 (br s, 2H), 2.34 - 2.18 (m, 2H), 1.88 - 1.65 (m, 4H), 1.62 - 1.31 (m, 3H), 0.70 (br s, 1H), 0.39 (br d, J = 7.6 Hz, 2H), 0.19 - 0.00 (m, 2H).

[00076] To afforad 5-chloro-N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (10.42 mg, 25.61 umol, 3.47% yield) as white solid. MS (ESI) m/z 407.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 13.44 (br s, 1H), 8.86 (br d, J = 7.6 Hz, 1H), 8.35 (br d, J = 8.0 Hz, 1H), 7.52 (br s, 1H), 7.42 (s, 1H), 5.11 - 4.95 (m, 1H), 4.51 - 4.38 (m, 1H), 3.09 (br s, 2H), 2.26 - 2.08 (m, 2H), 1.89 - 1.66 (m, 4H), 1.63 - 1.34 (m, 3H), 0.69 (br s, 1H), 0.38 (br s, 2H), 0.09 (br d, J = 13.7 Hz, 2H).

[00077] To afford 5-chloro-N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (39.82 mg, 97.87 umol, 13.27% yield) as white solid. MS (ESI) m/z 407.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 13.45 (br s, 1H), 8.92 (br d, J = 7.2 Hz, 1H), 8.41 - 8.32 (m, 1H), 7.53 (br s, 1H), 7.43 (s, 1H), 5.07 - 4.83 (m, 1H), 4.45 (br d, J = 5.4 Hz, 1H), 3.09 (br s, 2H), 2.35 - 2.12 (m, 2H), 1.92 - 1.67 (m, 4H), 1.65 - 1.35 (m, 3H), 0.70 (br s, 1H), 0.38 (br s, 2H), 0.09 (br d, J = 16.8 Hz, 2H).

Example 252. Synthesis of viral protease inhibitor compound 870



Step 1: tert-butyl ((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate

[00078] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (5 g, 12.15 mmol, 1 *eq*) in NH_3/MeOH (7 M, 50 mL, 28.80 *eq*) was stirred at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give tert-butyl N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (4.8 g, crude) as a yellow solid. MS (ESI) *m/z* 397.2 $[M+H]^+$.

Step 2: tert-butyl ((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate

[00079] To a solution of tert-butyl N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (4.8 g, 12.11 mmol, 1 *eq*) in DCM (50 mL) was added burgess reagent (5.77 g, 24.21 mmol, 2 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was poured into H_2O 60 mL at 20 °C, and then extracted with DCM (60 mL * 3). The combined organic layers were washed with brine (60 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate = 1/0 to 0/1) to give tert-butyl N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (4.3 g, 11.36 mmol, 93.85% yield) as a white solid. MS (ESI) *m/z* 379.2 $[M+H]^+$.

Step 3: (S)-2-amino-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-3-cyclopropylpropanamide

[00080] A solution of tert-butyl N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]carbamate (2.5 g, 6.61 mmol, 1 *eq*) in EA (10 mL) and HCl/EtOAc (4 M, 10 mL, 6.06 *eq*) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue to give (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-cyclopropyl-propanamide (2 g, crude, HCl) as a white solid. MS (ESI) *m/z* 279.1 $[M+H]^+$.

Step 4: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-imidazole-2-carboxamide

[00081] To a solution of 1H-imidazole-2-carboxylic acid (267.03 mg, 2.38 mmol, 1 *eq*), (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-cyclopropyl-propanamide (1.5 g, 2.38 mmol, 50% purity, 1 *eq*, HCl), DMAP (873.15 mg, 7.15 mmol, 3 *eq*) in DCM (10 mL) was added EDCI (913.42 mg, 4.76 mmol, 2 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150*50mm* 10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 10%-40%,10min) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (130 mg, 293.22 umol, 12.31% yield, 84% purity) as a white solid. MS (ESI) *m/z* 373.1 $[M+H]^+$.

Step 5: N-(1-(((1S)-1-cyano-2-(2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-imidazole-2-carboxamide

[00082] N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (130 mg, 293.22 umol, 12.31% yield, 84% purity) was separated by SFC (column: DAICEL

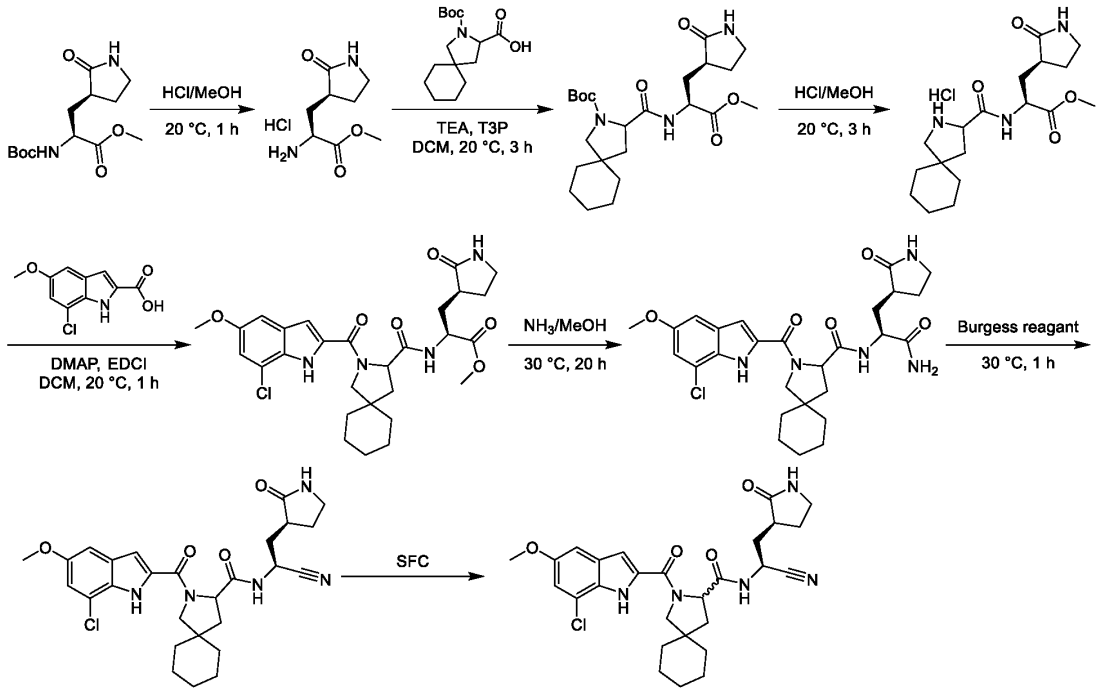
CHIRALPAK IG (250mm*30mm,10um);mobile phase: [Neu-MeOH];B%: 45%-45%,12min) to afford N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (14.9 mg, 40.01 umol, 11.46% yield, 100% purity) as a white solid. MS (ESI) *m/z* 373.2 $[M+H]^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.40 - 7.00 (m, 2H), 5.23 - 5.05 (m, 1H), 4.51 (t, *J* = 7.0Hz, 1H), 3.27 - 3.17 (m, 2H), 2.55 - 2.35 (m, 2H), 2.06 - 1.62 (m, 6H), 1.60 - 1.44 (m, 1H), 0.90 - 0.76 (m, 1H), 0.60 - 0.44 (m, 2H), 0.26 - 0.07 (m, 2H)

[00083] To give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (27.3 mg, 72.20 umol, 20.69% yield, 98.5% purity) as a white solid. MS (ESI) *m/z* 373.2 $[M+H]^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.43 - 7.01 (m, 2H), 5.06 (t, *J* = 7.3Hz, 1H), 4.56 (dd, *J* = 6.2, 7.4Hz, 1H), 3.29 - 3.19 (m, 2H), 2.48 - 2.39 (m, 1H), 2.34 (td, *J* = 6.7, 13.8Hz, 1H), 2.01 - 1.66 (m, 6H), 1.62 - 1.50 (m, 1H), 0.89 - 0.75 (m, 1H), 0.56 - 0.42 (m, 2H), 0.24 - 0.10 (m, 2H).

[00084] To give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (12.5 mg, 32.59 umol, 9.34% yield, 97.1% purity) as a white solid. MS (ESI) *m/z* 373.2 $[M+H]^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.33 - 7.09 (m, 2H), 5.15 - 5.03 (m, 1H), 4.53 (d, *J* = 6.0, 7.3Hz, 1H), 3.26 - 3.21 (m, 2H), 2.44 - 2.27 (m, 2H), 2.04 - 1.96 (m, 1H), 1.93 - 1.77 (m, 3H), 1.76 - 1.68 (m, 2H), 1.59 - 1.51 (m, 1H), 0.89 - 0.76 (m, 1H), 0.56 - 0.45 (m, 2H), 0.23 - 0.12 (m, 2H)

[00085] To give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-imidazole-2-carboxamide (5.5 mg, 13.32 umol, 3.82% yield, 90.2% purity) as a white solid. MS (ESI) *m/z* 373.2 $[M+H]^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.35 - 7.05 (m, 2H), 5.11 (t, *J* = 7.2Hz, 1H), 4.55 (t, *J* = 6.9Hz, 1H), 3.27 - 3.21 (m, 2H), 2.50 - 2.32 (m, 2H), 2.06 - 1.98 (m, 1H), 1.97 - 1.81 (m, 3H), 1.79 - 1.68 (m, 2H), 1.63 - 1.56 (m, 1H), 1.65 - 1.53 (m, 1H), 0.88 - 0.77 (m, 1H), 0.52 (d, *J* = 7.8Hz, 2H), 0.23 - 0.09 (m, 2H).

Example 253. Synthesis of viral protease inhibitor compound 896



Step 1: methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[00086] A mixture of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (2.6 g, 9.08 mmol, 1 *eq*) in HCl/MeOH (4 M, 30 mL, 13.21 *eq*) was stirred at 20 °C for 1.5 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (30 mL * 3) and concentrated under reduced pressure to get product methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (2 g, crude, HCl) as yellow oil. MS (ESI) *m/z* 187.1 $[M+H]^+$.

Step 2: tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate

[00087] To a mixture of methyl (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (2 g, 8.98 mmol, 1 *eq*, HCl) in DCM (20 mL) and DMF (2 mL) was added 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (2.80 g, 9.88 mmol, 1.1 *eq*), T3P (11.43 g, 17.96 mmol, 10.68 mL, 50% purity, 2 *eq*) and TEA (5.45 g, 53.89 mmol, 7.50 mL, 6 *eq*) was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The

combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 4/1~0/1) to get the product tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (2.5 g, 4.43 mmol, 49.31% yield, 80% purity) as white solid. MS (ESI) *m/z* 452.3 $[M+H]^+$.

Step 3: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[00088] A mixture of tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (2.1 g, 3.72 mmol, 80% purity, 1 *eq*) in HCl/MeOH (4 M, 25 mL, 26.88 *eq*) was stirred at 20 °C for 3 h. Upon completion, The mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to get the product methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.4 g, crude, HCl) as white oil. MS (ESI) *m/z* 352.2 $[M+H]^+$.

Step 4: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate

[00089] A mixture of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.4 g, 3.61 mmol, 1 *eq*, HCl) in DCM (20 mL) was added with 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (1.06 g, 4.69 mmol, 1.3 *eq*), DMAP (1.10 g, 9.02 mmol, 2.5 *eq*) and EDCI (1.38 g, 7.22 mmol, 2 *eq*), and then the resulting mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 2/1~0/1) to obtain methyl (2S)-2-[[2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.5 g, 2.68 mmol, 74.34% yield) as white solid. MS (ESI) *m/z* 559.2 $[M+H]^+$.

Step 5: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[00090] A mixture of methyl (2S)-2-[[2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (1.46 g, 2.61 mmol, 1 *eq*) in NH_3/MeOH (7 M, 20 mL, 53.61 *eq*) was stirred at 30 °C for 20 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (30 mL * 3) and concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.35 g, crude) as yellow oil. MS (ESI) *m/z* 544.2 $[M+H]^+$.

Step 6: 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[00091] To a mixture of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxopyrrolidin-3-yl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.35 g, 2.11 mmol, 85% purity, 1 *eq*) in DCM (15 mL) was added burgess reagent (1.51 g, 6.33 mmol, 3 *eq*) = at 30 °C for 1 h. Upon completion, the mixture were quenched with water (1 mL) and blow-dried with N_2. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 35% - 65%, 8 min), which was further separated by SFC (column: REGIS(S,S)WHELK-O1 (250 mm * 25 mm, 10 um); mobile phase: [Neu-ETOH]; B%: 60% - 60%, 12 min) to get the product 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (322.82 mg, 613.70 umol, 29.10% yield) as white solid. MS (ESI) *m/z* 526.2 $[M+H]^+$.

[00092] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.12 (d, *J*=1.7 Hz, 1H), 7.02 (s, 1H), 6.97 (br d, *J*=1.8 Hz, 1H), 5.12 - 5.00 (m, 1H), 4.62 (dd, *J*=7.9, 9.7 Hz, 1H), 3.92 (br d, *J*=10.3 Hz, 1H), 3.86 - 3.33 (m, 5H), 3.30 - 3.26 (m, 1H), 2.77 - 2.55 (m, 1H), 2.52 - 2.23 (m, 3H), 1.98 - 1.67 (m, 3H), 1.62 - 1.41 (m, 10H).

[00093] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.07 (br d, *J*=1.1 Hz, 1H), 8.72 (br d, *J*=7.5 Hz, 1H), 7.44 (br d, *J*=0.7 Hz, 1H), 7.12 (br s, 1H), 6.97 (s, 2H), 4.92 (br s, 1H), 4.60 (br s, 1H), 3.85 - 3.77 (m, 4H), 3.61 (br s, 1H), 3.14 (br s, 2H), 2.43 - 2.21

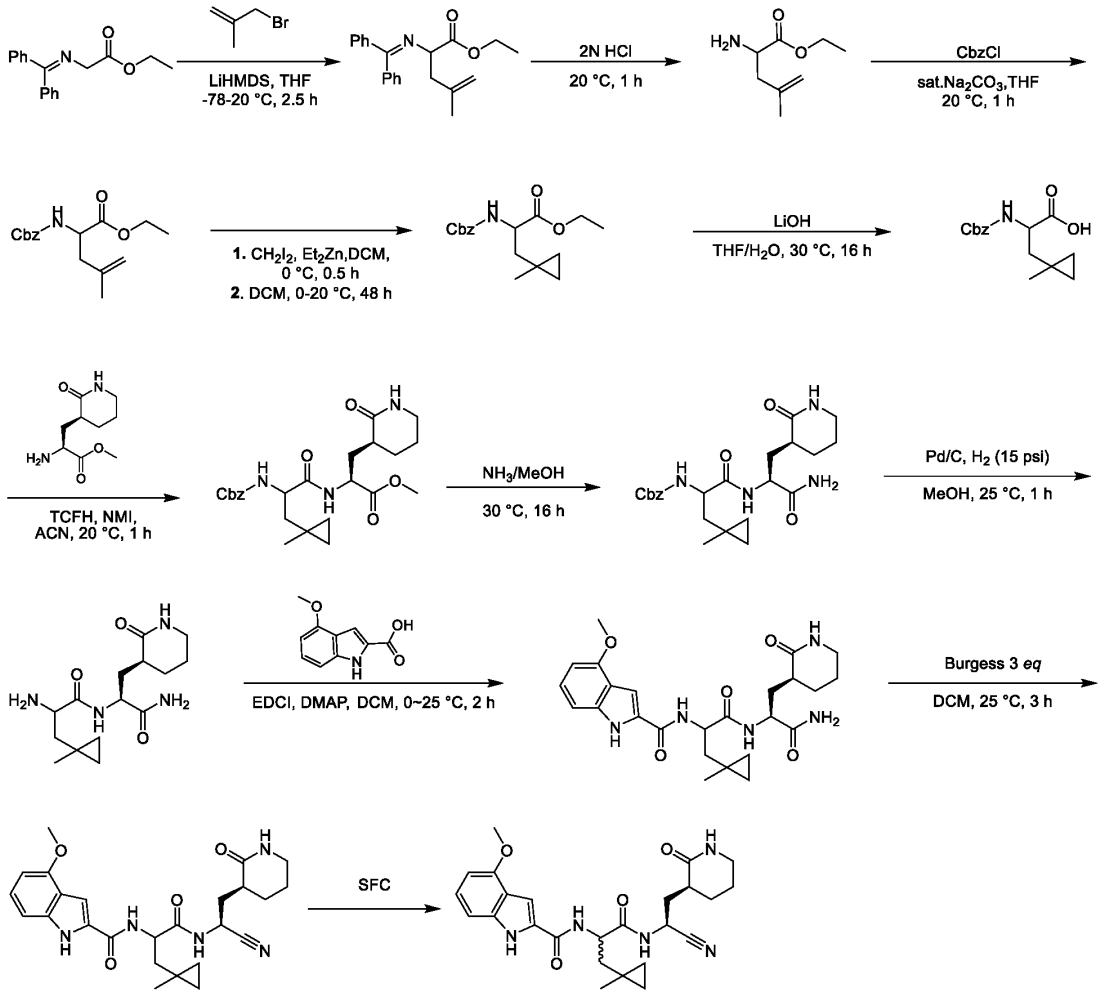
(m, 2H), 2.20 - 1.89 (m, 2H), 1.80 (br s, 1H), 1.72 - 1.58 (m, 2H), 1.57 - 1.35 (m, 10H).

[00094] To get the product 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (289.32 mg, 550.01 umol, 26.08% yield) as white solid. MS (ESI) *m/z* 526.2 $[M+H]^+$.

[00095] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.12 (d, *J*=2.0 Hz, 1H), 7.04 (s, 1H), 6.99 - 6.93 (m, 1H), 5.06 - 4.97 (m, 1H), 4.63 (dd, *J*=7.9, 9.5 Hz, 1H), 3.94 (br d, *J*=10.4 Hz, 1H), 3.88 - 3.68 (m, 4H), 3.30 - 2.73 (m, 2H), 2.68 - 2.10 (m, 4H), 1.94 - 1.69 (m, 3H), 1.62 - 1.40 (m, 10H).

[00096] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.46 - 10.49 (m, 1H), 8.67 (br d, *J*=6.6 Hz, 1H), 7.44 (br s, 1H), 7.21 - 7.07 (m, 1H), 6.98 (s, 2H), 5.06 - 4.83 (m, 1H), 4.59 (br dd, *J*=2.1, 4.1 Hz, 1H), 3.80 (s, 4H), 3.70 - 3.44 (m, 1H), 3.22 - 3.10 (m, 2H), 2.25 (s, 4H), 1.82 (br s, 1H), 1.68 (br d, *J*=10.4 Hz, 2H), 1.59 - 1.33 (m, 10H).

Example 254. Synthesis of viral protease inhibitor compound 910



Step 1: ethyl 2-((diphenylmethylene)amino)-4-methylpent-4-enoate

[00097] To a solution of ethyl 2-(benzhydrylideneamino)acetate (10 g, 37.41 mmol, 1 *eq*) in THF (40 mL) was added LiHMDS (1 M, 41.15 mL, 1.1 *eq*) dropwise (~0.5 h) at -78 °C under N_2, and then the mixture was stirred at -78 °C for 0.5 h. After the addition of 3-bromo-2-methyl-prop-1-ene (5.05 g, 37.41 mmol, 3.77 mL, 1 *eq*) dropwise to the mixture, the mixture was stirred at 0 °C for 0.5 h, and then the mixture was warmed to 20 °C and stirred at 20 °C for 1 h. Upon completion, the mixture was quenched by water (200 mL) and concentrated in vacuum. Then the mixture was extracted with EA (70 mL * 3), washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by column (SiO_2, PE:EA = 1:0 to 40:1) to obtained ethyl 2-((diphenylmethylene)amino)-4-methylpent-4-enoate

(9.5 g, 26.60 mmol, 71.11% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 322.2 $[M+H]^+$

Step 2: ethyl 2-amino-4-methylpent-4-enoate

[00098] A solution of ethyl 2-((diphenylmethylene)amino)-4-methylpent-4-enoate (9 g, 28.00 mmol, 1 *eq*) in aq. HCl (2 M, 140.01 mL, 10 *eq*) was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was concentrated in vacuum to obtained ethyl 2-amino-4-methylpent-4-enoate (9 g, crude) as a yellow gum. MS (ESI) *m/z* 158.2 $[M+H]^+$

Step 3: ethyl 2-(((benzyloxy)carbonyl)amino)-4-methylpent-4-enoate

[00099] To a solution of ethyl 2-amino-4-methylpent-4-enoate (9 g, 28.62 mmol, 1 *eq*) in THF (100 mL) was added sat.Na_2CO_3 (7.21 g, 68.06 mmol, 14.84 uL, 2.38 *eq*) (adjust pH=8), and then benzyl carbonochloridate (9.77 g, 57.25 mmol, 8.14 mL, 2 *eq*) was added. The resulting mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was concentrated in vacuum, then was added H_2O (500 mL) and extracted with EA (150 mL * 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, purified by column (SiO_2, PE:EA = 60:1 to 40:1) and re-purified by prep-HPLC (column: Xtimate C18 10u 250mm * 80mm; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-65%,30min) to obtained ethyl 2-(((benzyloxy)carbonyl)amino)- 4-methylpent-4-enoate (3.4 g, 10.50 mmol, 36.69% yield, 90% purity) as a yellow oil. MS (ESI) *m/z* 292.1 $[M+H]^+$

Step 4: ethyl 2-(((benzyloxy)carbonyl)amino)-3-(1-methylcyclopropyl)propanoate

[000100] To a solution of $ZnEt_2$ (1 M, 14.27 mL, 4.16 *eq*) in DCM (50 mL) at 0 °C under N_2 was added diiodomethane (3.79 g, 14.17 mmol, 1.14 mL, 4.13 *eq*) in DCM (25 mL) dropwise, then the mixture was stirred at 0 °C under N_2 for 0.5 h, then was added ethyl 2-(((benzyloxy)carbonyl)amino)- 4-methylpent-4-enoate (1 g, 3.43 mmol, 1 *eq*) in DCM (25 mL) at 0 °C. The mixture was stirred at 20 °C for 48 h. Upon the reaction completion, the mixture was poured into aq. HCl (30 mL, 1 M) at 0 °C, then was extracted with DCM (10 mL * 3), the organic phase was dried with Na_2SO_4, concentrated in vacuum and purified by column (SiO_2, PE:EA = 60:1 to 30:1) to obtained ethyl 2-(((benzyloxy)carbonyl)amino)-3-(1-methylcyclopropyl)propanoate

(800 mg, 2.36 mmol, 68.69% yield, 90% purity) as a yellow oil. MS (ESI) *m/z* 306.1 $[M+H]^+$

Step 5: 2-(((benzyloxy)carbonyl)amino)-3-(1-methylcyclopropyl)propanoic acid

[000101] To a solution of ethyl 2-(((benzyloxy) carbonyl) amino)-3-(1-methylcyclopropyl) propanoate (800 mg, 2.62 mmol, 1 *eq*) in THF (5 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (329.81 mg, 7.86 mmol, 3 *eq*), the mixture was stirred at 30 °C for 16 h. Upon the reaction completion, the mixture was adjust pH=1 with aq.HCl (1M, 10 mL) and was extracted with ethyl acetate (5 mL * 2). The resulting mixture was concentrated in vacuum to obtained 2-(((benzyloxy)carbonyl)amino)-3-(1-methylcyclopropyl)propanoic acid (700 mg, crude) as a light yellow oil. MS (ESI) *m/z* 276.1 $[M-H]^+$

Step 6: (2S)-methyl 2-(2-(((benzyloxy)carbonyl)amino)-3-(1-methylcyclopropyl)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000102] A solution of 2-(((benzyloxy)carbonyl)amino)-3-(1-methylcyclopropyl)propanoic acid (600 mg, 2.16 mmol, 1 *eq*) in ACN (1 mL) was added methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (614.54 mg, 2.60 mmol, 1.2 *eq*, HCl), [chloro(dimethylamino)methylene]-dimethyl-ammonium;hexafluorophosphate (910.59 mg, 3.25 mmol, 1.5 *eq*), then 1-methylimidazole (532.90 mg, 6.49 mmol, 517.37 uL, 3 *eq*), the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with 1 N HCl (10 mL), then washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 0:1 to 10:1) to give (2S)-methyl 2-(2-(((benzyloxy)carbonyl)amino)-3-(1-methylcyclopropyl)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1.1 g, 1.80 mmol, 82.98% yield, 75% purity) as yellow solid. MS (ESI) *m/z* 460.2 $[M+H]^+$.

Step 7: benzyl (1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)carbamate

[000103] A solution of (2S)-methyl 2-(2-(((benzyloxy)carbonyl)amino)-3-(1-methylcyclopropyl)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate (1 g, 1.63

mmol, 75% purity, 1 *eq*) in NH_3/MeOH (7 M, 10.71 mL, 45.95 *eq*) was stirred at 30 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give benzyl (1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)carbamate (1 g, crude) as yellow solid. MS (ESI) *m/z* 445.2 $[M+H]^+$.

Step 8: 2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-(1-methylcyclopropyl)propanamide

[000104] A solution of benzyl (1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)carbamate (1 g, 2.25 mmol, 1 *eq*) in IPA (20 mL) was added HCl (12 M, 243.71 uL, 1.3 *eq*), Pd/C (1 g, 833.33 umol, 10% purity, 0.37 *eq*) under N_2. The suspension was degassed under vacuum and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 psi) at 25 °C for 1 h. Upon completion, the reaction mixture was filtered through celatom then concentrated under reduced pressure to give 2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-(1-methylcyclopropyl)propanamide (680 mg, crude) as yellow solid. MS (ESI) *m/z* 311.2 $[M+H]^+$.

Step 9: N-(1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000105] To a solution of 2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-(1-methylcyclopropyl)propanamide (680 mg, 1.96 mmol, 1 *eq*, HCl) in DCM (7 mL) was added 4-methoxy-1H-indole-2-carboxylic acid (449.78 mg, 2.35 mmol, 1.2 *eq*), DMAP (718.54 mg, 5.88 mmol, 3 *eq*), then EDCI (751.65 mg, 3.92 mmol, 2 *eq*) at 0 °C, the mixture was then stirred at 25 °C for 2 h. Upon completion, the mixture was quenched with water (10 mL) and extracted with DCM (10 mL* 3). The organic layers were washed with 1N HCl (10 mL) and then brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 0:1 to 10:1) to give N-(1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (550 mg, 1.02 mmol, 52.21% yield, 90% purity) as yellow solid. MS (ESI) *m/z* 484.2 $[M+H]^+$.

Step 10: N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000106] A mixture of N-(1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (550 mg, 1.02 mmol, 90% purity, 1 *eq*) in DCM (1 mL) was added burgess reagent (731.85 mg, 3.07 mmol, 3 *eq*) and stirred at 25 °C for 3 h. Upon completion, the reaction mixture was quenched by addition H_2O (0.5 mL) at 20 °C, and then concentrated under reduced pressure (<30 °C) to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250*50mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-55%,10min) to give N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (250 mg, 531.64 umol, 51.93% yield, 99% purity) as white solid. MS (ESI) *m/z* 466.2 $[M+H]^+$.

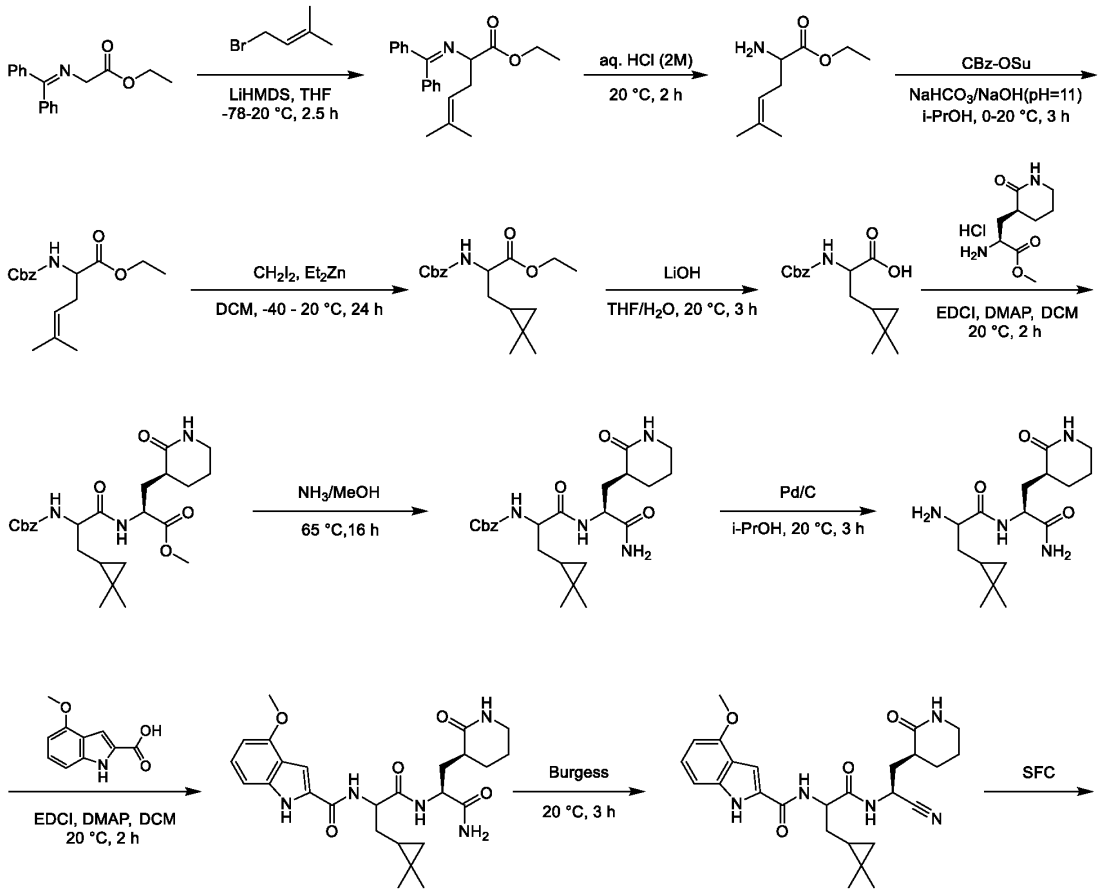
Step 11: N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000107] N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (250 mg, 531.64 umol, 99% purity, 1 *eq*) was purified by SFC (column: DAICEL CHIRALPAK AD (250 mm* 30 mm, 10 um); mobile phase: [Neu-ETOH]; B%: 50% - 50%, 15 min) to give N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (63.08 mg, 135.50 umol, 25.49% yield, 100% purity) as white solid. MS (ESI) *m/z* 466.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.58 (br s, 1H), 8.96 (br d, *J* = 8.1 Hz, 1H), 8.43 (br d, *J* = 7.8 Hz, 1H), 7.52 (br s, 1H), 7.33 (s, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 5.10 - 5.01 (m, 1H), 4.66 - 4.57 (m, 1H), 3.88 (s, 3H), 3.13 - 3.02 (m, 2H), 2.32 - 2.20 (m, 2H), 1.86 - 1.72 (m, 3H), 1.72 - 1.51 (m, 3H), 1.39 (br d, J = 11.0 Hz, 1H), 1.07 (s, 3H), 0.56 - 0.49 (m, 1H), 0.29 - 0.23 (m, 1H), 0.23 - 0.12 (m, 2H)

[000108] To give N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(1-methylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (85.13

mg, 182.86 umol, 34.40% yield, 100% purity) as white solid. MS (ESI) *m/z* 466.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.60 (br s, 1H), 8.95 (br d, J = 8.1 Hz, 1H), 8.45 (br d, J = 8.4 Hz, 1H), 7.53 (br s, 1H), 7.34 (s, 1H), 7.10 (t, J = 7.9 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 5.09 - 5.00 (m, 1H), 4.70 - 4.62 (m, 1H), 3.89 (s, 3H), 3.13 - 3.03 (m, 2H), 2.25 - 2.14 (m, 2H), 1.89 - 1.69 (m, 4H), 1.65 - 1.50 (m, 2H), 1.48 - 1.36 (m, 1H), 1.05 (s, 3H), 0.59 - 0.50 (m, 1H), 0.27 - 0.20 (m, 1H), 0.19 - 0.11 (m, 2H)

Example 255. Synthesis of viral protease inhibitor compound 912



Step 1: ethyl 2-((diphenylmethylene)amino)-5-methylhex-4-enoate

[000109] To a solution of ethyl 2-(benzhydrylideneamino) acetate (5 g, 18.70 mmol, 1 *eq*) in THF (50 mL) was added LiHMDS (1M, 20.57 mL, 1.1 *eq*) at -78 °C, stirred 30 min, and then 1-bromo-3-methyl-but-2-ene (2.79 g, 18.70 mmol, 2.16 mL, 1 *eq*) was

added. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O 50 mL at 20 °C, and then extracted with EtOAc (60 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 30/1) to give ethyl 2-(benzhydrylideneamino)-5-methyl-hex-4-enoate (3 g, 8.94 mmol, 47.82% yield) as a yellow oil. MS (ESI) *m/z* 336.2 $[M+H]^+$.

Step 2: ethyl 2-amino-5-methylhex-4-enoate

[000110] A solution of ethyl 2-(benzhydrylideneamino)-5-methyl-hex-4-enoate (2.7 g, 8.05 mmol, 1 *eq*) in HCl (2 M, 27 mL, 6.71 *eq*) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove H_2O to give ethyl 2-amino-5-methyl-hex-4-enoate (1.3 g, crude, HCl) as a white solid.

Step 3: ethyl 2-(((benzyloxy)carbonyl)amino)-5-methylhex-4-enoate

[000111] To a solution of ethyl 2-amino-5-methyl-hex-4-enoate (900 mg, 5.26 mmol, 1 *eq*) in IPA (10 mL) was added Na_2CO_3 (1.39 g, 13.14 mmol, 9 mL, 2.5 *eq*) and NaOH (210.22 mg, 5.26 mmol, 1 mL, 1 *eq*) to adjust pH to 11 at 0 °C, and then benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (1.44 g, 5.78 mmol, 1.1 *eq*) was added. The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was poured into H_2O 30 mL at 20 °C, and then extracted with EtOAc (35 mL * 3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give ethyl 2-(benzyloxycarbonylamino)-5-methyl-hex-4-enoate (1.3 g, crude) as a yellow solid. MS (ESI) *m/z* 306.1 $[M+H]^+$.

Step 4: ethyl 2-(((benzyloxy)carbonyl)amino)-3-(2,2-dimethylcyclopropyl)propanoate

[000112] To a solution of ethyl 2-(benzyloxycarbonylamino)-5-methyl-hex-4-enoate (1.2 g, 2.75 mmol, 70% purity, 1 *eq*) in DCM (20 mL) and $ZnEt_2$ (1 M, 6.88 mL, 2.5 *eq*) at -40 °C, stirred 10 min, then CH_2I_2 (1.47 g, 5.50 mmol, 443.83 uL, 2 *eq*) was added. The mixture was stirred at 20 °C for 15 h 50 min. Upon completion, the reaction mixture was quenched by addition NH_4Cl 30 mL at 20 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl

acetate = 80/1 to 40/1) to give ethyl 2-(benzyloxycarbonylamino)-3-(2,2-dimethylcyclopropyl)propanoate (1 g, crude) as a yellow oil. MS (ESI) *m/z* 320.2 $[M+H]^+$.

Step 5: 2-(((benzyloxy)carbonyl)amino)-3-(2,2-dimethylcyclopropyl)propanoic acid

[000113] To a solution of ethyl 2-(benzyloxycarbonylamino)-3-(2,2-dimethylcyclopropyl)propanoate (1 g, 3.13 mmol, 1 *eq*) in THF (9 mL) and H_2O (3 mL) was added $LiOH.H_2O$ (394.15 mg, 9.39 mmol, 3 *eq*). The mixture was stirred at 50 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. 1M HCl was added to adjust pH to 3, then extracted with DCM (35 mL * 3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-(benzyloxycarbonylamino)-3-(2,2-dimethylcyclopropyl)propanoic acid (1.1 g, crude) as a yellow oil.

Step 6: (2S)-methyl 2-(2-(((benzyloxy)carbonyl)amino)-3-(2,2-dimethylcyclopropyl)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000114] To a solution of 2-(benzyloxycarbonylamino)-3-(2,2-dimethylcyclopropyl)propanoic acid (1.08 g, 3.71 mmol, 1 *eq*), methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.75 g, 7.41 mmol, 2 *eq*, HCl) in DCM (10 mL) was added DMAP (1.13 g, 9.27 mmol, 2.5 *eq*), then EDCI (1.42 g, 7.41 mmol, 2 *eq*) was added. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O 50 mL at 20 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1/0 to 80/1) to give methyl (2S)-2-[[2-(benzyloxycarbonylamino)-3-(2,2-dimethylcyclopropyl)propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.5 g, 3.17 mmol, 85.45% yield) as a yellow solid. MS (ESI) *m/z* 474.2 $[M+H]^+$.

Step 7: benzyl (1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(2,2-dimethylcyclopropyl)-1-oxopropan-2-yl)carbamate

[000115] A solution of methyl (2S)-2-[[2-(benzyloxycarbonylamino)-3-(2,2-dimethylcyclopropyl)propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.5 g,

3.17 mmol, 1 *eq*) in NH_3/MEOH (7 M, 15.00 mL, 33.15 *eq*) was stirred at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove MeOH to give benzyl N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-[(2,2-dimethylcyclopropyl)methyl]-2-oxo-ethyl]carbamate (1.45 g, crude) as a yellow solid. MS (ESI) *m/z* 459.2 $[M+H]^+$.

Step 8: 2-amino-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-(2,2-dimethylcyclopropyl)propanamide

[000116] To a solution of benzyl N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-[(2,2-dimethylcyclopropyl)methyl]-2-oxo-ethyl]carbamate (1.45 g, 3.16 mmol, 1 *eq*) in i-PrOH (15 mL) was added HCl (12 M, 263.51 uL, 1 *eq*), then Pd/C (1.45 g, 3.16 mmol, 20% purity, 1 *eq*) was added. The mixture was stirred at 20 °C for 3 h under H_2. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give (2S)-2-[[2-amino-3-(2,2-dimethylcyclopropyl)propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanamide (1 g, crude) as a yellow solid. MS (ESI) *m/z* 325.2 $[M+H]^+$.

Step 9: N-(1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-(2,2-dimethylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000117] To a solution of (2S)-2-[[2-amino-3-(2,2-dimethylcyclopropyl)propanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanamide (990 mg, 3.05 mmol, 1 *eq*), 4-methoxy-1H-indole-2-carboxylic acid (700.10 mg, 3.66 mmol, 1.2 *eq*) in DCM (10 mL) was added DMAP (932.03 mg, 7.63 mmol, 2.5 *eq*), then EDCI (1.17 g, 6.10 mmol, 2 *eq*) was added. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O 25 mL at 20 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (25 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100/0 to 95/5) to give N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-[(2,2-dimethylcyclopropyl)methyl]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (1.01 g, 2.03 mmol, 66.52% yield) as a yellow solid. MS (ESI) *m/z* 498.2 $[M+H]^+$.

Step 10: N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-dimethylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000118] To a solution of N-[2-[[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-[(2,2-dimethylcyclopropyl)methyl]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (1 g, 2.01 mmol, 1 *eq*) in DCM (10 mL) was added burgess reagent (957.85 mg, 4.02 mmol, 2 *eq*). The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was poured into H_2O 30 mL at 20 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4 filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250*50mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-65%,10min) to give N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-dimethylcyclopropyl)methyl]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (280 mg, 583.86 umol, 29.05% yield, 100% purity) as a white solid. MS (ESI) *m/z* 480.2 $[M+H]^+$.

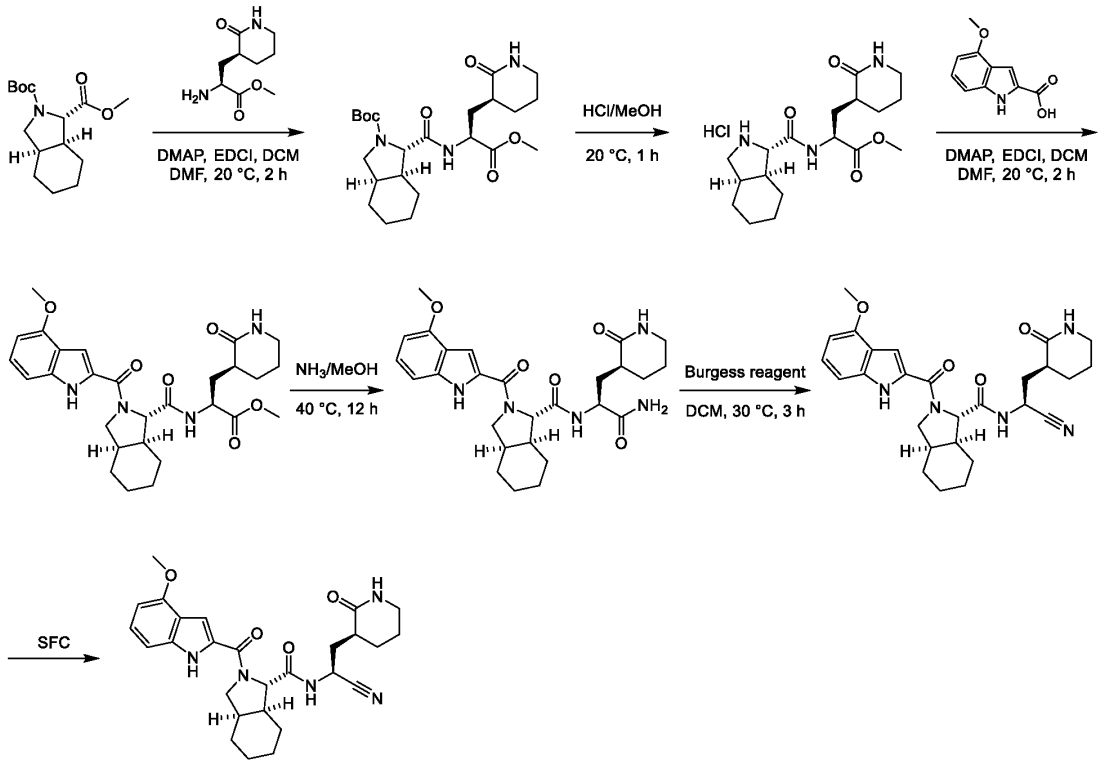
Step 11: N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-dimethylcyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000119] N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-dimethylcyclopropyl)methyl]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (280 mg, 583.86 umol, 29.05% yield, 100% purity) was separated by SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [Neu-IPA];B%: 30%-50%,18min) to give N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-dimethylcyclopropyl)methyl]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (55 mg, 113.31 umol, 19.41% yield, 98.8% purity) as a white solid. MS (ESI) *m/z* 480.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.26 (s, 1H), 7.19 - 7.10 (m, 1H), 7.07 - 6.98 (m, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 5.17 - 5.08 (m, 1H), 4.58 - 4.46 (m, 1H), 3.93 (s, 3H), 3.27 - 3.15 (m, 2H), 2.55 - 2.39 (m, 2H), 2.08 - 1.89 (m, 3H), 1.86 - 1.66 (m, 3H), 1.56 - 1.45 (m, 1H), 1.26 - 0.96 (m, 6H), 0.71 - 0.58 (m, 1H), 0.50 (d, *J* = 2.5, 4.5 Hz, 1H), 0.14 - 0.01 (m, 1H).

[000120] To give N-[2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-dimethylcyclopropyl)methyl]-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (155

mg, 322.56 umol, 55.25% yield, 99.8% purity) as a white solid. MS (ESI) *m/z* 480.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.27 (s, 1H), 7.19 - 7.11 (m, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.06 (d, *J* = 6.2, 10.0 Hz, 1H), 4.59 (d, *J* = 5.8, 8.4 Hz, 1H), 3.93 (s, 3H), 3.22 - 3.11 (m, 2H), 2.40 (d, *J* = 6.2, 10.2, 13.8 Hz, 1H), 2.33 - 2.22 (m, 1H), 2.12 - 2.02 (m, 1H), 2.00 - 1.85 (m, 2H), 1.84 - 1.73 (m, 2H), 1.61 (d, *J* = 2.4 Hz, 1H), 1.49 (d, *J* = 11.0 Hz, 1H), 1.14 - 1.07 (m, 3H), 1.07 - 0.99 (m, 3H), 0.69 - 0.58 (m, 1H), 0.48 (d, *J* = 4.3, 8.7 Hz, 1H), 0.14 - 0.03 (m, 1H).

Example 256. Synthesis of viral protease inhibitor compound 918



Step 1: (1S,3aR,7aS)-tert-butyl 1-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)hexahydro-1H-isoindole-2(3H)-carboxylate

[000121] To a solution of (1S,3aR,7aS)-2-tert-butoxycarbonyl-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxylic acid (450 mg, 1.67 mmol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (571.23 mg, 2.17 mmol, 90% purity, 1.3 eq, HCl) in DCM (5 mL) and DMF (1.5 mL) was added DMAP (612.36 mg, 5.01 mmol, 3 eq) and EDCI (640.58 mg, 3.34 mmol, 2 eq), then the mixture was stirred at

20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 5:1 to 0:1) to give the product tert-butyl (1S,3aR,7aS)-1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-1,3,3a,4,5,6,7,7a-octahydroisoindole-2-carboxylate (680 mg, 1.36 mmol, 81.12% yield, 90% purity) as a white solid. MS (ESI) *m/z* 452.2 $[M+H]^+$.

[000122] Step 2: (S)-methyl 2-((1S,3aR,7aS)-octahydro-1H-isoindole-1-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate hydrochloride

[000123] To a solution of tert-butyl (1S,3aR,7aS)-1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-1,3,3a,4,5,6,7,7a-octahydroisoindole-2-carboxylate (680 mg, 1.51 mmol, 1 eq) in HCl/MeOH (4 M, 10 mL, 26.56 eq), and the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-[[(1S,3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydro-1H-isoindole-1-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (580 mg, crude, HCl) as a white solid.

[000124] Step 3: (S)-methyl 2-((1S,3aR,7aS)-2-(4-methoxy-1H-indole-2-carbonyl)octahydro-1H-isoindole-1-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000125] To a solution of 4-methoxy-1H-indole-2-carboxylic acid (371.62 mg, 1.94 mmol, 1.3 eq) and methyl (2S)-2-[[(1S,3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydro-1H-isoindole-1-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (580 mg, 1.50 mmol, 1 eq, HCl) in DCM (15 mL) and DMF (3 mL) was added DMAP (548.02 mg, 4.49 mmol, 3 eq) and EDCI (573.27 mg, 2.99 mmol, 2 eq), then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 5:1 to 0:1) to give the product methyl (2S)-2-[[(1S,3aR,7aS)-2-(4-methoxy-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (710 mg, 1.26 mmol, 84.18% yield, 93% purity) as a yellow solid. MS (ESI) *m/z* 525.2 $[M+H]^+$.

[000126] Step 4: (1S,3aR,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)octahydro-1H-isoindole-1-carboxamide

[000127] To a solution of methyl (2S)-2-[[(1S,3aR,7aS)-2-(4-methoxy-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (710 mg, 1.35 mmol, 1 eq) in NH_3/MeOH (7 M, 10 mL, 51.72 eq) and then mixture was stirred at 40 °C fo 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product (1S,3aR,7aS)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide (640 mg, crude) as a white solid. MS (ESI) *m/z* 510.2 $[M+H]^+$.

[000128] Step 5: (1S,3aR,7aS)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)octahydro-1H-isoindole-1-carboxamide

[000129] To a solution of (1S,3aR,7aS)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide (640 mg, 1.26 mmol, 1 eq) and BURGESS REAGENT (598.57 mg, 2.51 mmol, 2 eq) in DCM (10 mL), and the mixture was stirred at 30 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150 * 50 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 25% - 55%, 10 min) to give the product (1S,3aR,7aS)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide (450 mg, 906.26 umol, 72.16% yield, 99% purity) as a white solid. MS (ESI) *m/z* 492.2 $[M+H]^+$.

[000130] Step 6: 2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

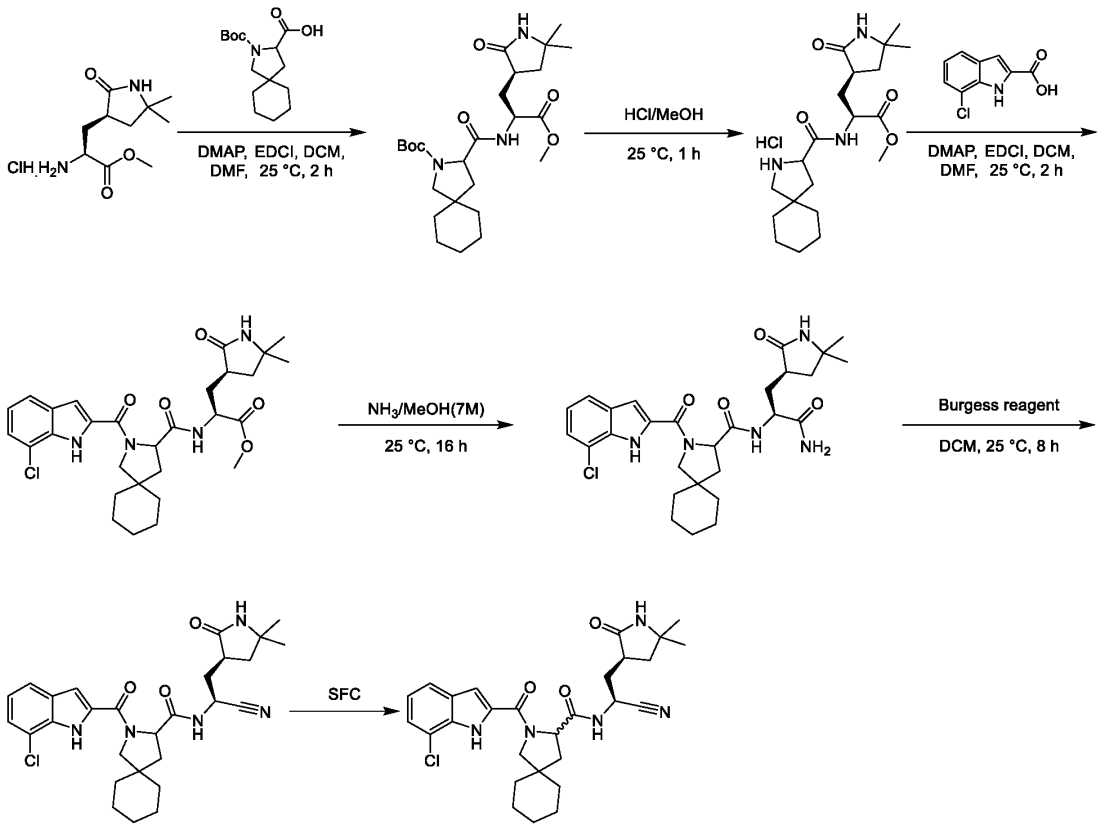
[000131] 2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide was purified by SFC (column: REGIS(S,S) WHELK-O1(250 mm * 25 mm, 10 um); mobile phase: [0.1% NH_3H_2O MEOH]; B%: 50% - 50%, 4 min) to give the product (3aR,7aS)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide Isomer 1 (136.17 mg, 277.00 umol, 30.26% yield, 100% purity) as a white solid MS (ESI) *m/z* 492.2 $[M+H]^+$.

[000132] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.56 (s, 1H), 9.30 - 8.85 (m, 1H), 7.54 (br s, 1H), 7.15 - 7.07 (m, 1H), 7.07 - 6.95 (m, 2H), 6.52 (d, J = 7.6 Hz, 1H), 5.06 (br d, J = 7.7 Hz, 1H), 4.58 - 4.20 (m, 1H), 4.06 - 3.94 (m, 1H), 3.91 - 3.81 (m, 3H), 3.78 (br dd, J = 5.8, 9.8 Hz, 1H), 3.15 - 2.89 (m, 2H), 2.45 - 2.37 (m, 1H), 2.31 - 2.11 (m, 3H), 1.46 (br d, J = 3.5 Hz, 13H).

[000133] To give the product (3aR,7aS)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide Isomer 2 (161.76 mg, 329.06 umol, 35.95% yield, 100% purity) as a white solid. MS (ESI) *m/z* 492.2 $[M+H]^+$.

[000134] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.62 - 11.55 (m, 1H), 9.15 - 8.84 (m, 1H), 7.55 - 7.39 (m, 1H), 7.15 - 7.09 (m, 1H), 7.06 - 6.97 (m, 2H), 6.61 - 6.50 (m, 1H), 5.05 (br d, J = 8.1 Hz, 1H), 4.47 - 4.24 (m, 1H), 4.00 (dd, J = 7.1, 9.7 Hz, 1H), 3.90 - 3.83 (m, 3H), 3.82 - 3.75 (m, 1H), 3.08 (br s, 2H), 2.44 - 2.37 (m, 1H), 2.24 (br d, J = 7.1 Hz, 3H), 1.83 - 1.32 (m, 13H).

Example 257. Synthesis of viral protease inhibitor compound 930



Step 1: tert-butyl 3-[[(1S)-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate

[000135] To a mixture of methyl (2S)-2-amino-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (750.00 mg, 2.99 mmol, 1 *eq*, HCl) and 2-tert-butoxycarbonyl-2-azaspiro[4.5]decane-3-carboxylic acid (932.40 mg, 3.29 mmol, 1.1 *eq*) in DCM (10 mL) and DMF (3 mL) was added DMAP (1.10 g, 8.97 mmol, 3 *eq*) and EDCI (1.15 g, 5.98 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was diluted with H_2O 30 mL and extracted with EA 60 mL (20 mL * 3). The combined organic layers were washed with brine 30 mL (30 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 0/1) to give tert-butyl 3-[[(1S)-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (1.2 g, 2.50 mmol, 83.64% yield) as a yellow oil. MS (ESI) *m/z* 480.3 $[M+H]^+$

Step 2: methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate

[000136] A mixture of tert-butyl 3-[[(1S)-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (1.2 g, 2.50 mmol, 1 *eq*) in HCl/MeOH (20 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (1 g, 2.40 mmol, 96.09% yield, HCl) as a yellow solid.

Step 3: methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate

[000137] To a mixture of 7-chloro-1H-indole-2-carboxylic acid (427.50 mg, 2.19 mmol, 1 *eq*) and methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (1 g, 2.40 mmol, 1.1 *eq*, HCl) in DCM (12 mL) and DMF (3 mL) was added DMAP (801.02 mg, 6.56 mmol, 3 *eq*) and EDCI (837.95 mg, 4.37 mmol, 2 *eq*), the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O 30 mL and extracted with EA 60 mL (20 mL * 3). The combined organic layers were washed with brine 30 mL (30 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 0/1) to give methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (700 mg, 1.26 mmol, 57.49% yield) as a white solid. MS (ESI) *m/z* 557.3$[M+H]^+$

Step 4: N-[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo-ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

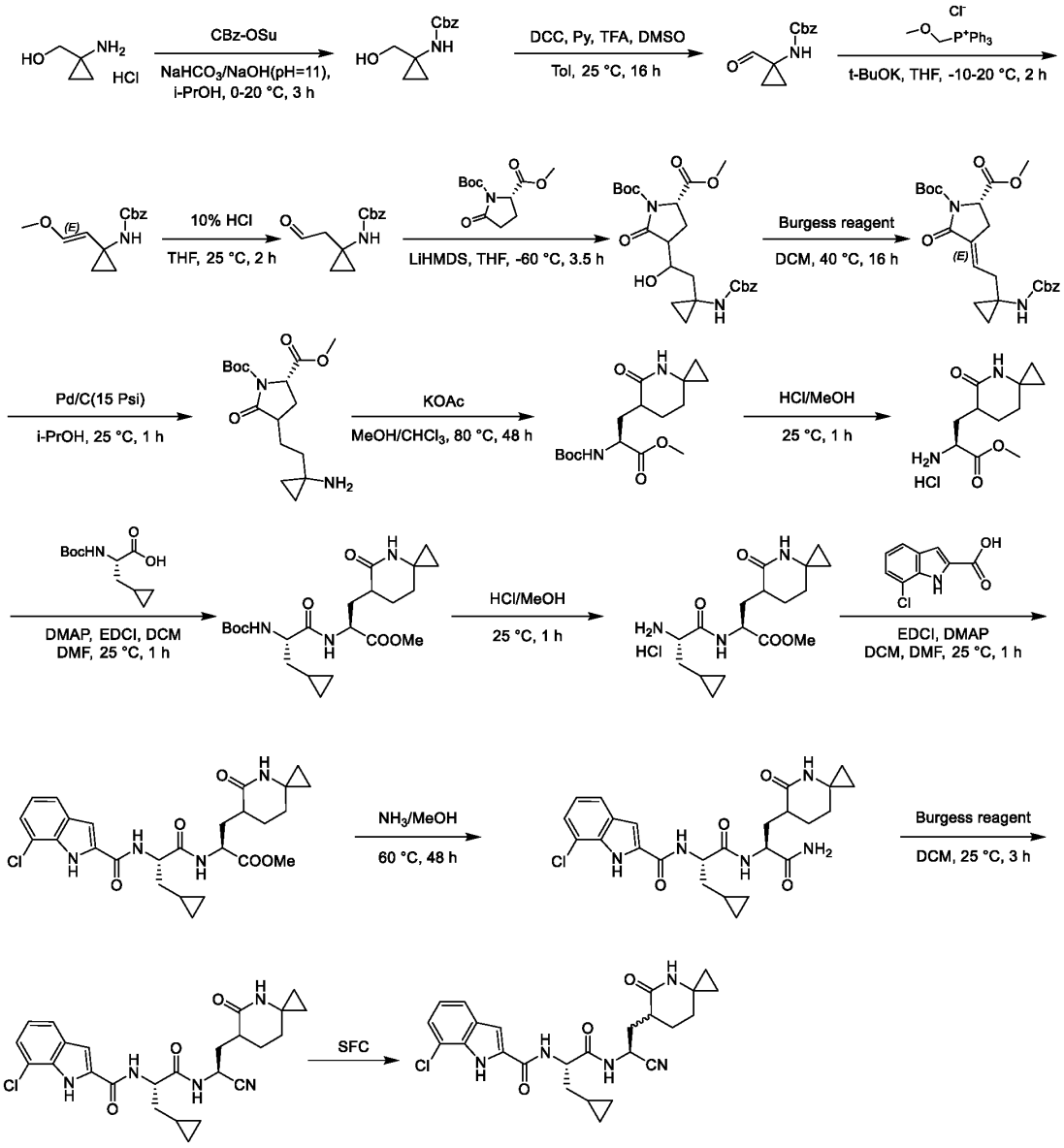
[000138] A mixture of methyl (2S)-2-[[2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (700 mg, 1.26 mmol, 1 *eq*) in NH_3/MeOH (7 M, 105.00 mL, 334.25 *eq*) was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo-ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-

carboxamide (660 mg, 1.22 mmol, 96.90% yield) as a white solid. MS (ESI) *m/z* 542.3 $[M+H]^+$

Step 5: 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[000139] A mixture of N-[(1S)-2-amino-1-[(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)methyl]-2-oxo-ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (660 mg, 1.03 mmol, 85% purity, 1 *eq*) in DCM (10 mL) was added Burgess reagent (863.22 mg, 3.62 mmol, 3.5 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 8 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 40%-60%,8min) to give desired compound (270 mg, yield 49%, purity 100%) as a white solid, which was further separated by SFC (condition:column: DAICEL CHIRALPAK IC(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 43%-43%,7min) to give 2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)ethyl]-2-azaspiro[4.5]decane-3-carboxamide (100 mg, 190.82 umol, 18.44% yield) as a white solid. MS (ESI) *m/z* 524.2$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.66 - 11.45 (m, 1H), 8.95 (d, *J* = 8.2 Hz, 1H), 7.81 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.14 (s, 1H), 7.11 - 6.97 (m, 1H), 4.99 - 4.75 (m, 1H), 4.50 (t, *J* = 8.6 Hz, 1H), 3.83 (br d, *J* = 10.1 Hz, 1H), 3.66 (d, *J* = 10.4 Hz, 1H), 2.76 - 2.64 (m, 1H), 2.29 - 2.13 (m, 2H), 1.99 (dd, *J* = 8.6, 11.9 Hz, 1H), 1.82 - 1.66 (m, 1H), 1.65 - 1.28 (m, 12H), 1.18 - 1.07 (m, 3H), 1.02 (s, 3H)

Example 258. Synthesis of viral protease inhibitor compound 934



Step 1: benzyl N-[1-(hydroxymethyl)cyclopropyl]carbamate

[000140] 350 mL of a buffer-pH=11(Saturated $NaHCO_3$ adjusted with 4 M NaOH to pH=11) was added to a solution of (1-aminocyclopropyl) methanol (20 g, 229.57 mmol, 1 *eq*) in IPA (350 mL). The reaction mixture was cooled to 0 °C and benzyl 2, 5-dioxopyrrolidine-1-carboxylate (53.54 g, 229.57 mmol, 1 *eq*) was added. The reaction mixture was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was filtered and then concentrated under reduced pressure to remove IPA. The residue was diluted with H_2O 100 mL and extracted with EA 200 mL (100 mL * 2). The

combined organic layers were washed with brine 100 mL (100 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with DCM at 20 °C for 20 min. Compound benzyl N-[1-(hydroxymethyl)cyclopropyl]carbamate (35 g, 142.37 mmol, 62.02% yield, 90% purity) was obtained as a white solid.

Step 2: benzyl N-(1-formylcyclopropyl) carbamate

[000141] To a mixture of benzyl N-[1-(hydroxymethyl) cyclopropyl] carbamate (13 g, 58.76 mmol, 1 *eq*) in toluene (130 mL) and DMSO (130.00 g, 1.66 mol, 130.00 mL, 28.32 *eq*) was added TFA (3.35 g, 29.38 mmol, 2.18 mL, 0.5 *eq*) and pyridine (4.65 g, 58.76 mmol, 4.74 mL, 1 *eq*) and DCC (36.37 g, 176.27 mmol, 35.66 mL, 3 *eq*). The mixture was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was filtered and diluted with EA 100 mL and washed with H_2O 300 mL (100 mL * 3). The combined organic layers were washed with brine 100 mL (100 mL * 1), and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 8/1 to 5/1) to give benzyl N-(1-formylcyclopropyl) carbamate (9 g, 39.00 mmol, 66.37% yield, 95% purity) as a white solid.

Step 3: benzyl N-[1-[(E)-2-methoxyvinyl] cyclopropyl] carbamate

[000142] To a solution of methoxymethyl (triphenyl) phosphonium; chloride (25.02 g, 72.98 mmol, 4 *eq*) in THF (80 mL) was added a solution of t-BuOK (1 M, 72.80 mL, 3.99 *eq*) drop-wise at -10 °C. The reaction mixture was warmed to 20 °C and stirred at 20 °C for 1 h. Benzyl N-(1-formylcyclopropyl)carbamate (4 g, 18.25 mmol, 1 *eq*) in THF (40 mL) was added at 0 °C, the solution was stirred at 20 °C for another 1 h under N_2. Upon completion, the reaction mixture was diluted with H_2O 100 mL and extracted with ethyl acetate 200 mL (100 mL * 2). The combined organic layers were washed with brine 100 mL (100 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 30/1 to 10/1) to give benzyl N-[1-[(E)-2-methoxyvinyl] cyclopropyl] carbamate (2.1 g, 7.64 mmol, 41.89% yield, 90% purity) as a yellow oil. MS (ESI) *m/z* 246.1 $[M-H]^+$

Step 4: benzyl N-[1-(2-oxoethyl)cyclopropyl]carbamate

[000143] To a mixture of benzyl N-[1-[(E)-2-methoxyvinyl] cyclopropyl] carbamate (1.9 g, 7.68 mmol, 1 *eq*) in THF (20 mL) was added HCl (19.38 g, 53.15 mmol, 19.00 mL, 10% purity, 6.92 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O 100 mL and extracted with EA 300 mL (150 mL * 2). The combined organic layers were washed with brine 300 mL (300 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 5/1). Compound benzyl N-[1-(2-oxoethyl) cyclopropyl] carbamate (1.3 g, 5.02 mmol, 65.28% yield, 90% purity) was obtained as a white solid.

Step 5: O1-tert-butyl O2-methyl (2S)-4-[2-[1-(benzyloxycarbonylamino)cyclopropyl]-1-hydroxy- ethyl]-5-oxo-pyrrolidine-1,2-dicarboxylate

[000144] To a mixture of O1-tert-butyl O2-methyl (2S)-5-oxopyrrolidine-1, 2-dicarboxylate (450 mg, 1.85 mmol, 1 *eq*) in THF (8 mL) was added LiHMDS (1 M, 2.40 mL, 1.3 *eq*) in one portion at -60 °C under N_2. The mixture was stirred at -60 °C for 30 min, and then benzyl N-[1-(2-oxoethyl)cyclopropyl]carbamate (431.51 mg, 1.85 mmol, 1 *eq*) in THF (4 mL) was added at - 60 °C and stirred for 2 h at -60 °C. Upon completion, the reaction mixture was quenched by addition AcOH 4 mL in THF 8 mL at -60 °C and concentrated under reduced pressure to give a residue and used next step directly. Compound O1-tert-butyl O2-methyl (2S)-4-[2-[1-(benzyloxycarbonylamino) cyclopropyl]-1-hydroxy-ethyl] -5-oxo-pyrrolidine-1, 2-dicarboxylate (900 mg, crude) was obtained as a yellow oil. MS (ESI) *m/z* 377.1 $[M+H-100]^+$

Step 6: O1-tert-butyl O2-methyl(2S,4E)-4-[2-[1-(benzyloxycarbonylamino)cyclopropyl]ethylidene]- 5-oxo-pyrrolidine-1,2-dicarboxylate

[000145] To a mixture of O1-tert-butyl O2-methyl (2S)-4-[2-[1-(benzyloxycarbonylamino)cyclopropyl]-1-hydroxy-ethyl]-5-oxo-pyrrolidine-1,2-dicarboxylate (900 mg, 1.89 mmol, 1 *eq*) in DCM (20 mL) was added burgess reagent (1.35 g, 5.67 mmol, 3 *eq*) at 25 °C.The mixture was stirred at 40 °C for 16 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 3/1). Compound O1-tert-butyl O2-

methyl(2S,4E)-4-[2-[1-(benzyloxycarbonylamino)cyclopropyl]ethylidene]-5-oxo-pyrrolidine-1,2-dicarboxylate (420 mg, 824.42 umol, 43.65% yield, 90% purity) was obtained as a colorless oil. MS (ESI) *m/z* 459.2 $[M+H]^+$

Step 7: O1-tert-butyl O2-methyl (2S)-4-[2-(1-aminocyclopropyl)ethyl]-5-oxo-pyrrolidine-1,2-dicarboxylate

[000146] To a mixture of O1-tert-butyl O2-methyl (2S,4E)-4-[2-[1-(benzyloxycarbonylamino)cyclopropyl]ethylidene]-5-oxo-pyrrolidine-1,2-dicarboxylate (700 mg, 1.53 mmol, 1 *eq*) in i-PrOH (10 mL) was added Pd/C (300 mg, 1.53 mmol, 10% purity, 1.00 *eq*). The mixture was stirred at 25 °C for 1 h under H_2 (3.08 mg, 1.53 mmol, 1 *eq*) at 15 Psi. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue and used next step directly. Compound O1-tert-butyl O2-methyl (2S)-4-[2-(1-aminocyclopropyl)ethyl]-5-oxo-pyrrolidine-1,2-dicarboxylate (400 mg, crude) was obtained as a colourless oil.

Step 8: methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate

[000147] To a mixture of O1-tert-butyl O2-methyl (2S)-4-[2-(1-aminocyclopropyl)ethyl]-5-oxo-pyrrolidine-1,2-dicarboxylate (350 mg, 1.07 mmol, 1 eq) in MeOH (5 mL) and $CHCl_3$ (0.5 mL) was added KOAc (210.48 mg, 2.14 mmol, 2 eq) at 80 °C. The mixture was stirred at 80 °C for 48 h. Upon completion, the residue was diluted with H_2O 5 mL and extracted with EA 10 mL (5 mL * 2). The combined organic layers were washed with BRINE 10 mL (10 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue and used next step directly. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5:1 to 1:1). Compound methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5-oxo-4-azaspiro [2.5]octan-6-yl)propanoate (200 mg, 586.42 umol, 54.69% yield, 95.7% purity) was obtained as a colourless oil.

Step 9: methyl (2S)-2-amino-3-(5-oxo-4-azaspiro [2.5] octan-6-yl) propanoate

[000148] To methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate (170 mg, 520.85 umol, 1 *eq*) was added HCl/MeOH (4 M, 42.50 mL, 326.39 *eq*). The mixture was stirred at 25 °C for 60 min. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The

residue was used next step directly. Compound methyl (2S)-2-amino-3-(5-oxo-4-azaspiro [2.5] octan-6-yl) propanoate (136 mg, crude, HCl) was obtained as colourless oil.

Step 10: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]- 3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate

[000149] To a mixture of methyl (2S)-2-amino-3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate (136 mg, 517.64 umol, 1 *eq*, HCl) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (118.68 mg, 517.64 umol, 1 *eq*) in DCM (9 mL) was added DMAP (126.48 mg, 1.04 mmol, 2 *eq*) and EDCI (198.46 mg, 1.04 mmol, 2 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O 20 mL and extracted with EA 40 mL (20 mL * 2). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5:1/1 to 1/1). Compound methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate (186 mg, 403.86 umol, 78.02% yield, 95% purity) was obtained as a colourless oil. MS (ESI) *m/z* 438.3 $[M+H]^+$

Step 11: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.5] octan-6-yl)propanoate

[000150] To methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4 -azaspiro[2.5]octan-6-yl)propanoate (162 mg, 370.26 umol, 1 *eq*) was added HCl/MeOH (4 M, 12.21 mL, 131.86 *eq*). The mixture was stirred at 25 °C for 60 min. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was used next step directly. Compound methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.5] octan-6-yl)propanoate (138 mg, crude, HCl) was obtained as a white solid.

[000151] Step 12: methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl] amino]-3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate

[000152] To a mixture of 7-chloro-1H-indole-2-carboxylic acid (72.20 mg, 369.11 umol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate (138 mg, 369.11 umol, 1 *eq*, HCl) in DCM (5 mL) was added EDCI (141.52 mg, 738.22 umol, 2 *eq*) and DMAP (90.19 mg, 738.22 umol, 2 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O 20 mL and extracted with EA 40 mL (20 mL * 2). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 to 1/1). Compound methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate (150 mg, 282.52 umol, 76.54% yield, 97% purity) was obtained as a colourless oil. MS (ESI) *m/z* 515.2 $[M+H]^+$

Step 13: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(5-oxo-4-azaspiro[2.5]octan-6-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000153] A solution of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-(5-oxo-4-azaspiro[2.5]octan-6-yl)propanoate (130 mg, 254.61 umol, 1 *eq*) in NH_3/MeOH (7 M, 13.16 mL, 361.91 *eq*) was stirred at 60 °C for 48 h. Upon completion, the reaction mixture concentrated under reduced pressure to give a residue and used next step directly. Compound N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(5-oxo-4-azaspiro[2.5]octan-6-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (120 mg, 217.93 umol, 85.59% yield, 90% purity) was obtained as a white solid. MS (ESI) *m/z* 500.2 $[M+H]^+$

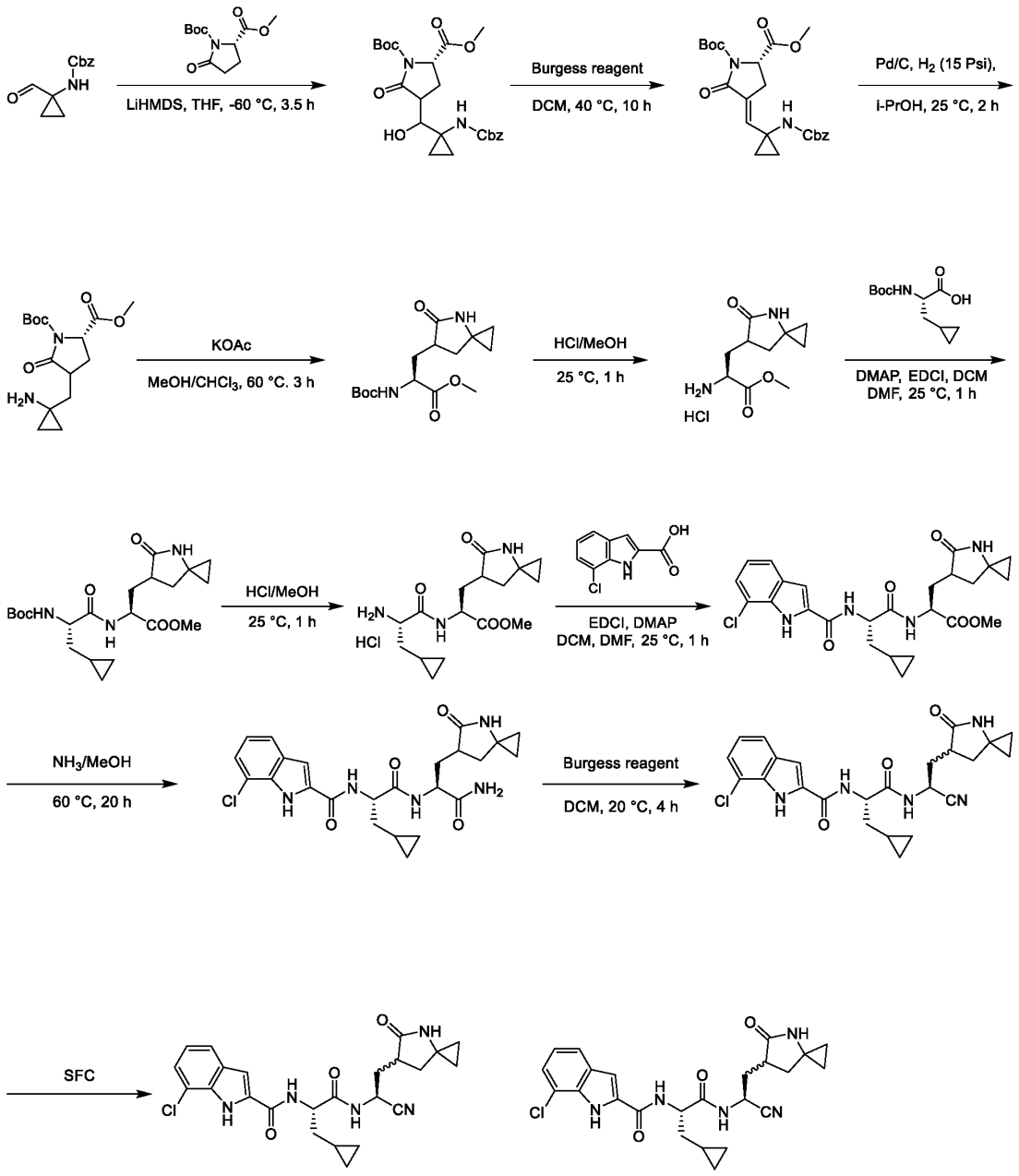
Step 14: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(5-oxo-4-azaspiro[2.5]octan-6-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000154] To a mixture of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(5-oxo-4-azaspiro[2.5]octan-6-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (120 mg, 240.01 umol, 1 *eq*) in DCM (6 mL) was added burgess reagent (114.39 mg, 480.01 umol, 2 *eq*). The mixture was stirred at

25 °C for 3 h. Upon completion, the reaction mixture was diluted with H_2O 5 mL and extracted with DCM 10 mL (5 mL * 2). The combined organic layers were concentrated by blow-drying to give a residue. The residue was purified by neutral prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-55%, 10 min) to get the mixture 50 mg. The 50 mg mixture was purified by SFC (column: DAICEL CHIRALPAK IF (250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O ETOH];B%: 40%-40%,12min). Compound 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(5-oxo-4-azaspiro[2.5]octan-6-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (12 mg, 24.65 umol, 10.27% yield, 99% purity) was obtained as white solid. MS (ESI) *m/z* 482.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.73 (br s, 1H), 9.02 (d, *J* = 8.1 Hz, 1H), 8.72 (d, *J* = 7.7 Hz, 1H), 7.67 - 7.57 (m, 2H), 7.35 - 7.29 (m, 1H), 7.26 (s, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 5.09 (q, *J* = 8.0 Hz, 1H), 4.59 - 4.47 (m, 1H), 2.40 - 2.21 (m, 2H), 1.98 - 1.71 (m, 4H), 1.63 - 1.33 (m, 3H), 0.88 - 0.65 (m, 2H), 0.61 - 0.37 (m, 5H), 0.26 - 0.03 (m, 2H).

[000155] 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(5-oxo-4-azaspiro[2.5]octan-6-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (4 mg, 8.30 umol, 3.46% yield) were obtained as white solid. MS (ESI) *m/z* 482.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.73 (br d, *J* = 1.8 Hz, 1H), 9.04 (br d, *J* = 7.5 Hz, 1H), 8.75 (br d, *J* = 7.9 Hz, 1H), 7.71 - 7.54 (m, 2H), 7.35 - 7.23 (m, 2H), 7.07 (t, *J* = 7.8 Hz, 1H), 5.02 (q, *J* = 7.2 Hz, 1H), 4.61 - 4.51 (m, 1H), 2.35 - 2.26 (m, 2H), 2.01 - 1.91 (m, 1H), 1.87 - 1.71 (m, 3H), 1.67 - 1.40 (m, 3H), 0.88 - 0.65 (m, 2H), 0.62 - 0.37 (m, 5H), 0.26 - 0.06 (m, 2H).

Example 259. Synthesis of viral protease inhibitor compound 936



Step 1: O1-tert-butyl O2-methyl (2S)-4-[[1-(benzyloxycarbonylamino)cyclopropyl]-hydroxy-methyl]-5-oxo-pyrrolidine-1,2-dicarboxylate

[000156] To a solution of benzyl N-(1-formylcyclopropyl)carbamate (1.80 g, 8.22 mmol, 1 *eq*) in THF (30 mL) was added LiHMDS (1 M, 10.69 mL, 1.3 *eq*) at -60°C. The solution was stirred for 1 h at -60°C. O1-tert-butyl O2-methyl (2S)-5-oxopyrrolidine-1,2-dicarboxylate (2000 mg, 8.22 mmol, 1 *eq*) was added. The solution was stirred for

2.5 h at -60 °C. Upon completion, the solution was quenched with H_2O(60mL) and extracted with EA(50mL*3) and concentrated to give crude O1-tert-butyl O2-methyl (2S)-4-[[1-(benzyloxycarbonylamino)cyclopropyl]-hydroxy-methyl]-5-oxo-pyrrolidine-1,2-dicarboxylate (3.3 g, crude) as a yellow oil. The crude was used directly for the next step. MS (ESI) *m/z* 463.2 $[M+H]^+$

Step 2: O1-tert-butyl O2-methyl (2S,4E)-4-[[1-(benzyloxycarbonylamino)cyclopropyl]methylene]-5-oxo-pyrrolidine-1,2-dicarboxylate

[000157] To a solution of O1-tert-butyl O2-methyl (2S)-4-[[1-(benzyloxycarbonylamino)cyclopropyl]-hydroxy-methyl]-5-oxo-pyrrolidine-1,2-dicarboxylate (3300 mg, 7.14 mmol, 1 *eq*) in DCM (50 mL) was added burgess reagent (5.10 g, 21.41 mmol, 3 *eq*) at 20 °C. The solution was stirred for 10 h at 40°C. Upon completion, the solution was concentrated to give crude. The crude was purified by column (SiO_2, PE: EA=10:1 to 0:1) to give product O1-tert-butyl O2-methyl (2S,4E)-4-[[1-(benzyloxycarbonylamino)cyclopropyl]methylene]-5-oxo-pyrrolidine-1,2-dicarboxylate (1.9 g, 4.27 mmol, 59.91% yield) as a yellow. MS (ESI) *m/z* 445.1 $[M+H]^+$

Step 3: O1-tert-butyl O2-methyl (2S)-4-[(1-aminocyclopropyl)methyl]-5-oxo-pyrrolidine-1,2-dicarboxylate

[000158] To a solution of O1-tert-butyl O2-methyl (2S,4E)-4-[[1-(benzyloxycarbonylamino)cyclopropyl]methylene]-5-oxo-pyrrolidine-1,2-dicarboxylate (1400 mg, 3.15 mmol, 1 *eq*) in IPA (25 mL) was added Pd/C (261.12 mg, 220.48 umol, 10% purity, 0.07 *eq*) (10%) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 psi) at 25 °C for 2 h. Upon completion, the mixture was filtered and concentrated to give crude O1-tert-butyl O2-methyl (2S)-4-[(1-aminocyclopropyl)methyl]-5-oxo-pyrrolidine-1,2-dicarboxylate (950 mg, crude) was obtained as a yellow oil. The crude was used directly for the next step. MS (ESI) *m/z* 313.1 $[M+H]^+$

Step 4: methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate

[000159] To a solution of O1-tert-butyl O2-methyl (2S)-4-[(1-aminocyclopropyl)methyl]-5-oxo-pyrrolidine-1,2-dicarboxylate (950 mg, 3.04 mmol, 1 *eq*) in MeOH (15 mL)

and $CHCl_3$ (1.5 mL) was added KOAc (895.46 mg, 9.12 mmol, 3 *eq*). The solution was stirred for 3 h at 60 °C. Upon completion, the solution was concentrated and diluted with H_2O (50mL) and extracted with EA (50mL*3) and concentrated to give crude. The crude was purified by column (SiO_2, PE: EA=10:1 to 0:1) to give product methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (430 mg, 1.38 mmol, 45.26% yield) was obtained as a white solid. MS (ESI) *m/z* 313.1 $[M+H]^+$

Step 5: methyl (2S)-2-amino-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate

[000160] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (260 mg, 832.37 umol, 1 *eq*) in HCl/MeOH (10 mL) was stirred for 1 h at 25 °C. Upon completion, the solution was concentrated to dryness to give crude methyl (2S)-2-amino-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (207 mg, crude, HCl) as a white solid. The crude was used directly for the next step. MS (ESI) *m/z* 213.2 $[M+H]^+$

Step 6: methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate

[000161] To a solution of methyl (2S)-2-amino-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (207 mg, 832.31 umol, 1 *eq*, HCl) in DCM (7 mL) was added DMAP (203.37 mg, 1.66 mmol, 2 *eq*) and (2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (200.37 mg, 873.92 umol, 1.05 *eq*) and EDCI (319.11 mg, 1.66 mmol, 2 *eq*). The solution was stirred for 2 h at 20 °C. Upon completion, the solution was diluted with H_2O (40mL) and extracted with EA (50mL*3) and concentrated to give crude. The crude was purified by column (SiO_2, PE: EA=10:1 to 0:1) to give product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (290 mg, 684.77 umol, 82.27% yield) as a white solid. MS (ESI) *m/z* 424.2 $[M+H]^+$

Step 7: methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate

[000162] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (285 mg, 672.96 umol, 1 *eq*) in HCl/MeOH (10 mL) was stirred for 1 h at 25 °C. Upon

completion, The solution was concentrated to dryness to give crude methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (245 mg, crude, HCl) as a white solid. The crude was used directly for the next step. MS (ESI) *m/z* 324.2 $[M+H]^+$

Step 8: methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate

[000163] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (240 mg, 666.95 umol, 1 *eq*, HCl) in DCM (6 mL) was added DMAP(162.96 mg, 1.33 mmol, 2 *eq*) and 7-chloro-1H-indole-2-carboxylic acid (130.46 mg, 666.95 umol, 1 *eq*) and EDCI (255.71 mg, 1.33 mmol, 2 *eq*). The solution was stirred for 1 h at 25 °C Upon completion, The solution was diluted with H_2O (60mL) and extracted with EA(50mL*3) and concentrated to give crude. The crude was purified by column (SiO_2, PE:EA=10:1 to 0:1) to give product methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (185 mg, 369.28 umol, 55.37% yield) as an off-yellow solid. MS (ESI) m/z 501.2 [M+H]+

Step 9: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(5-oxo-4-azaspiro[2.4]heptan-6-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide

[000164] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-(5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (185 mg, 369.28 umol, 1 *eq*) in NH_3/MeOH (7 M, 10.55 mL, 200 *eq*) was stirred for 20 h at 60°C. Upon completion, The solution was concentrated to dryness to give crudeN-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(5-oxo-4-azaspiro[2.4]heptan-6-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (184 mg, crude) as a white solid. The crude was used directly for the next step. MS (ESI) m/z 486.2 [M+H]+

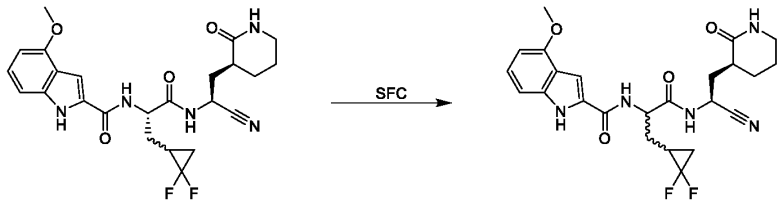
Step 10: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(5-oxo-4-azaspiro[2.4]heptan-6-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide

[000165] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[(5-oxo-4-azaspiro[2.4]heptan-6-yl)methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-1H-indole-2-carboxamide (155 mg, 318.95 umol, 1 *eq*) in DCM (15 mL) was added burgess reagent (228.03 mg, 956.86 umol, 3 *eq*) at 20 °C. The solution was stirred for 4 h at 20 °C. Upon completion, the solution was concentrated to give crude. The crude was purified by pre-TLC(SiO_2, PE:EA=0:1) to give product(70mg) and continued to purified by SFC to give product

[000166] 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(5-oxo-4-azaspiro[2.4]heptan-6-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (27 mg, 57.70 umol, 18.09% yield, 100% purity) as a white solid and 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-(5-oxo-4-azaspiro[2.4]heptan-6-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-1H-indole-2-carboxamide (5 mg, 10.36 umol, 3.25% yield, 97% purity) as a white solid. SFC method(neutral) column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [Neu-IPA];B%: 45%-45%,6min. MS (ESI) *m/z* 468.2 $[M+H]^+$ Isomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.72 (br s, 1H), 9.02 (d, *J* = 8.1 Hz, 1H), 8.72 (d, *J* = 7.5 Hz, 1H), 7.80 (s, 1H), 7.63 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.33 - 7.24 (m, 2H), 7.07 (t, *J* = 7.8 Hz, 1H), 5.01 - 4.93 (m, 1H), 4.55 - 4.47 (m, 1H), 3.50 - 3.37 (m, 1H), 3.33 - 3.27 (m, 1H), 2.68 - 2.59 (m, 1H), 2.56 - 2.51 (m, 1H), 2.20 (ddd, *J* = 5.7, 9.1, 13.7 Hz, 1H), 2.01 - 1.76 (m, 4H), 1.50 (ddd, *J* = 6.2, 7.6, 14.0 Hz, 1H), 1.03 (d, *J* = 6.1 Hz, 1H), 0.86 - 0.76 (m, 1H), 0.76 - 0.67 (m, 1H), 0.58 - 0.48 (m, 3H), 0.48 - 0.38 (m, 2H), 0.23 - 0.15 (m, 1H), 0.15 - 0.07 (m, 1H)

[000167] Isomer 2: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.74 (br s, 1H), 9.09 (d, *J* = 7.7 Hz, 1H), 8.76 (d, *J* = 7.7 Hz, 1H), 7.85 (s, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.26 (s, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 4.96 (d, *J* = 7.2 Hz, 1H), 4.58 (br d, *J* = 6.1 Hz, 1H), 3.56 - 3.38 (m, 2H), 2.58 (br s, 1H), 2.55 - 2.52 (m, 1H), 2.32 - 2.23 (m, 1H), 2.12 - 2.05 (m, 1H), 2.03 - 1.93 (m, 1H), 1.88 - 1.73 (m, 2H), 1.54 (s, 1H), 1.23 (br s, 1H), 1.03 (d, *J* = 6.1 Hz, 1H), 0.80 (br s, 1H), 0.77 - 0.71 (m, 1H), 0.61 - 0.48 (m, 3H), 0.48 - 0.39 (m, 2H), 0.19 (br d, *J* = 2.4 Hz, 1H), 0.12 (br d, *J* = 2.4 Hz, 1H)

Example 260. Synthesis of viral protease inhibitor compound 1059

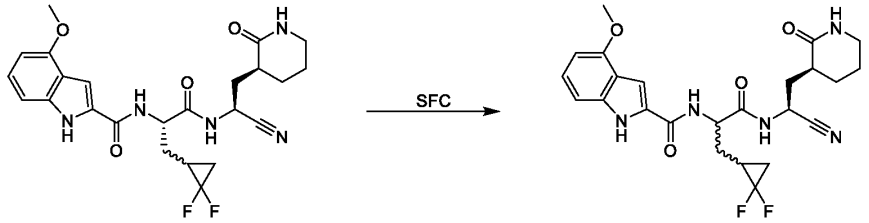


Step 1: N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000168] *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxoethyl]-4-methoxy-1*H*-indole-2-carboxamide (210 mg) was separated by SFC (column: DAICEL CHIRALPAK IE (250 mm * 30 mm, 10 um); mobile phase: [Heptane-EtOH]; B%: 40%-80%, 19 min) to give *N*-(1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide Isomer 1 (50 mg, 102.56 umol, 100% purity) as a white solid. MS (ESI) *m/z* 488.1 $[M+H]^+$ ^1H NMR (400 MHz, MeOD-d_4) δ = 7.27 (s, 1H), 7.20 - 7.10 (m, 1H), 7.04 - 7.02 (m, 1H), 6.52 - 6.50 (m, 1H), 5.17 - 5.08 (m, 1H), 4.60 - 4.56 (m, 1H), 3.93 (s, 3H), 3.26 - 3.18 (m, 2H), 2.53 - 2.37 (m, 2H), 2.49 - 2.40 (m, 1H), 2.04 - 1.88 (m, 3H), 1.87 - 1.64 (m, 3H), 1.58 - 1.43 (m, 2H), 1.18 - 1.05 (m, 1H).

[000169] Another purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 15%-55%, 8 min) to give *N*-(1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide Isomer 2 (25 mg, 47.03 umol, 91.7% purity) as a white solid. MS (ESI) *m/z* 488.1 $[M+H]^+$ ^1H NMR (400 MHz, MeOD-d_4) δ = 7.27 (s, 1H), 7.20 - 7.11 (m, 1H), 7.04 - 7.02 (m, 1H), 6.52 - 6.50 (m, 1H), 5.18 - 5.06 (m, 1H), 4.62 - 4.59 (m, 1H), 3.93 (s, 3H), 3.26 - 3.17 (m, 2H), 2.52 - 2.37 (m, 2H), 2.23 - 2.10 (m, 1H), 2.02 - 1.88 (m, 3H), 1.86 - 1.76 (m, 1H), 1.75 - 1.62 (m, 2H), 1.59 - 1.44 (m, 2H), 1.21 - 1.09 (m, 1H).

Example 261. Synthesis of viral protease inhibitor compound 1059

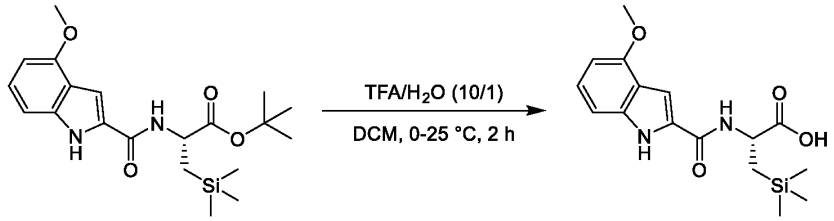


Step 1: N-(1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000170] *N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-[(2,2-difluorocyclopropyl)methyl]-2-oxoethyl]-4-methoxy-1*H*-indole-2-carboxamide (210 mg) was separated by SFC (column: DAICEL CHIRALPAK IE (250 mm * 30 mm, 10 um); mobile phase: [Heptane-EtOH]; B%: 40%-70%, 20 min) to give *N*-(1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide Isomer 2_2 (50 mg, 102.15 umol, 99.6% purity) as a white solid. MS (ESI) *m/z* 488.1 $[M+H]^+$ ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.27 (s, 1H), 7.18 - 7.16 (m, 1H), 7.04 - 7.02 (m, 1H), 6.53 - 6.51 (m, 1H), 5.08 - 5.04 (m, 1H), 4.64 - 4.60 (m, 1H), 3.98 (s, 3H), 3.20 - 3.19 (m, 2H), 2.39 - 2.33 (m, 2H), 2.31 - 2.05 (m, 5H), 2.01 - 1.96 (m, 2H), 1.72 - 1.43 (m, 2H), 1.18 - 1.09 (m, 1H).

[000171] Another purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 15%-55%, 8 min) to give *N*-(1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-(2,2-difluorocyclopropyl)-1-oxopropan-2-yl)-4-methoxy-1*H*-indole-2-carboxamide Isomer 2_1 (50 mg, 102.56 umol, 100% purity) as a white solid. MS (ESI) *m/z* 488.1 $[M+H]^+$ ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.27 (s, 1H), 7.20 - 7.11 (m, 1H), 7.04 - 7.02 (m, 1H), 6.52 - 6.50 (m, 1H), 5.18 - 5.06 (m, 1H), 4.62 - 4.59 (m, 1H), 3.93 (s, 3H), 3.26 - 3.17 (m, 2H), 2.52 - 2.37 (m, 2H), 2.23 - 2.10 (m, 1H), 2.02 - 1.88 (m, 3H), 1.86 - 1.76 (m, 1H), 1.75 - 1.62 (m, 2H), 1.59 - 1.44 (m, 2H), 1.16 - 1.12 (m, 1H).

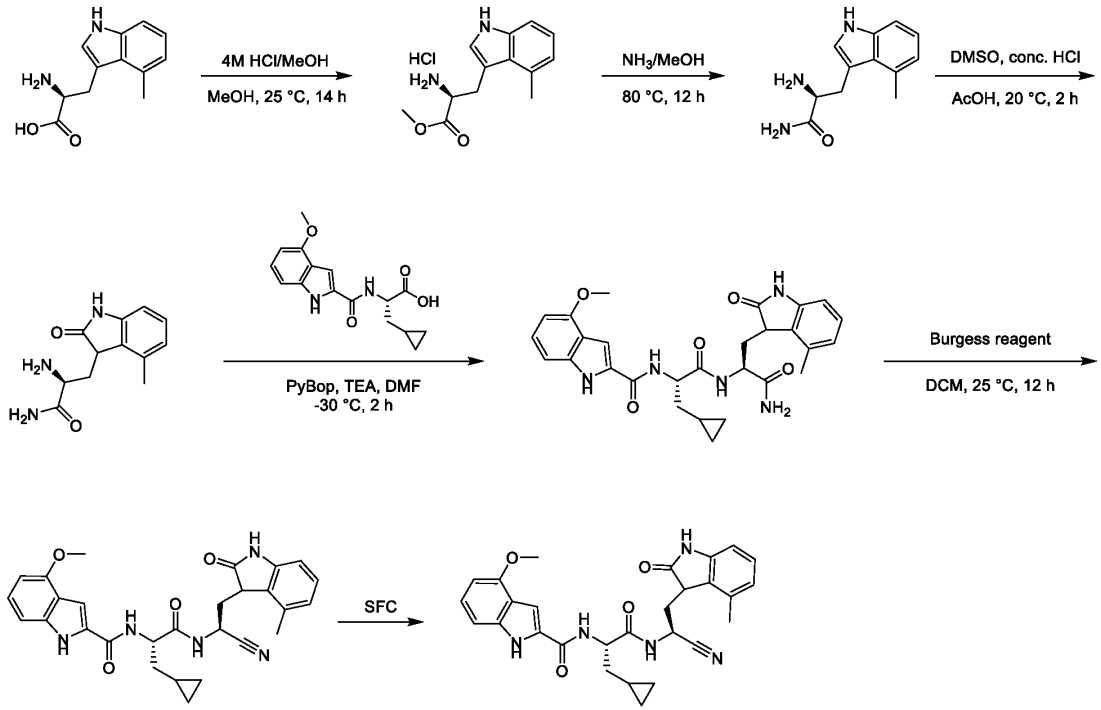
Example 262. Synthesis of (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoic acid



Step 1: (R)-2-(4-methoxy-1H-indole-2-carboxamido)-3-(trimethylsilyl)propanoic acid

[000172] A solution of tert-butyl (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoate (30 mg, 76.82 umol, 1 *eq*) in DCM (1.2 mL) was cooled to 0 °C, and then TFA/H_2O 10:1 (0.8 mL) was added dropwise at 0 °C. Then the reaction was stirred at 25 °C for 2 h. Upon completion, the reaction was concentrated in vacuum to dryness below 30 °C. The residue was poured into water (20 mL) .The aqueous phase was extracted with ethyl acetate (12 mL * 2). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 80 * 40 mm * 3 um; mobile phase: [water (0.04%HCl)-ACN]; B%: 32%-58%, 7 min) to give (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoic acid (2.74 mg, 8.19 umol, 10.67% yield, 100% purity) as a white solid. MS (ESI) *m/z* 335.1 $[M+H]^+$ ^1H NMR (400MHz, $CDCl_3$-*d*) δ = 9.81 - 9.58 (s, 1H), 7.21 (t, J=8.0 Hz, 1H), 7.09 - 7.02 (m, 2H), 6.60 (br d, J=7.9 Hz, 1H), 6.51 (d, J=7.8 Hz, 1H), 4.94 - 4.74 (m, 1H), 3.96 (s, 3H), 1.37 (dd, J=5.6, 14.7 Hz, 1H), 1.16 (br dd, J=9.7, 14.7 Hz, 1H), 0.11 (s, 9H)

Example 263. Synthesis of viral protease inhibitor compound 1083



Step 1: methyl (2S)-2-amino-3-(4-methyl-1H-indol-3-yl)propanoate

[000173] To (2S)-2-amino-3-(4-methyl-1H-indol-3-yl)propanoic acid (500 mg, 2.29 mmol, 1 *eq*) was added HCl/MeOH (4 M, 25.00 mL, 43.65 *eq*) in one portion at 20 °C under N_2. The mixture was stirred at 20 °C for 12 h. Upon completion, the reaction mixture was concentrated to get the product. Methyl (2S)-2-amino-3-(4-methyl-1H-indol-3-yl) propanoate (550 mg, 2.05 mmol, 89.33% yield, HCl) was obtianed as the purple solid and used directly next step. MS (ESI) *m/z* 233.1 $[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.03 (br s, 1 H), 8.49 (br s, 4 H), 7.09 - 7.22 (m, 2 H), 6.92 (t, J = 7.61 Hz, 1 H), 6.71 (d, J = 7.06 Hz, 1 H), 4.11 (br t, J = 7.28 Hz, 1 H), 3.65 (s, 3 H), 3.39 - 3.48 (m, 1 H), 3.27 (br d, J = 8.16 Hz, 1 H), 2.59 (s, 3 H)

Step 2: (2S)-2-amino-3-(4-methyl-1H-indol-3-yl) propanamide

[000174] To methyl (2S)-2-amino-3-(4-methyl-1H-indol-3-yl)propanoate (550 mg, 2.05 mmol, 1 *eq*, HCl) was added NH_3/MeOH (7 M, 20.00 mL, 68.41 *eq*) in one portion at 20 °C under N_2. The mixture was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was cooled to 25°C and concentrated to get the product. (2S)-2-amino-3-(4-methyl-1H-indol-3-yl) propanamide (520 mg, crude) was obtained as the light yellow solid and used directly next step. MS (ESI) *m/z* 218.1 $[M+H]^+$

Step 3: (2S)-2-amino-3-(4-methyl-2-oxo-indolin-3-yl)propanamide

[000175] To a mixture of (2S)-2-amino-3-(4-methyl-1H-indol-3-yl)propanamide (490 mg, 2.26 mmol, 1 *eq*) in AcOH (10 mL) was added the solution of DMSO (264.32 mg, 3.38 mmol, 264.32 uL, 1.5 *eq*) and HCl (12 M, 751.77 uL, 4 *eq*) in one portion at 20 °C under N_2. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was added the water (10 mL) and concentrated to 10 mL. The crude product was purified by pre-HPLC (column: Phenomenex luna C18 250*50 mm*10 um; mobile phase: [water (0.04%HCl)-ACN]; B%: 1% - 30%,10min). (2S)-2-amino-3-(4-methyl-2-oxo-indolin-3-yl) propanamide (124 mg, crude, HCl) was obtained as light green solid. MS (ESI) *m/z* 234.1 $[M+H]^+$

Step 4: N-[(1S)-2-[[(1S)-2-amino-1-[(4-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000176] To a mixture of (2S)-2-amino-3-(4-methyl-2-oxo-indolin-3-yl)propanamide (120 mg, 514.43 umol, 1 *eq*) and (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (194.41 mg, 514.43 umol, 80% purity, 1 *eq*) in DMF (1.2 mL) was added PyBop (267.71 mg, 514.43 umol, 1 *eq*) and TEA (156.17 mg, 1.54 mmol, 214.81 uL, 3 *eq*) at -30 °C under N_2. The mixture was stirred at -30 °C for 2 h. Upon completion, the reaction mixture was quenched by addition water (10 mL) at 20 °C, and then diluted with DCM (10 mL) and extracted with DCM (5 mL * 2). The combined organic layers were concentrated under reduced pressure to give a residue. The crude product was purified by pre-TLC. N-[(1S)-2-[[(1S)-2-amino-1-[(4-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (130 mg, crude) was obtained as the light yellow solid. MS (ESI) *m/z* 518.2 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-1-cyano-2-(4-methyl-2-oxo-indolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo- ethyl]-4-methoxy-1H-indole-2-carboxamide

[000177] To a mixture of N-[(1S)-2-[[(1S)-2-amino-1-[(4-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (130 mg, 251.17 umol, 1 *eq*) in DCM (20 mL) was added Burgess reaction (179.57 mg, 753.51 umol, 3 *eq*) in one portion at 20 °C under N_2. The mixture was stirred at 20 °C for 12 h. Upon completion, the reaction mixture was

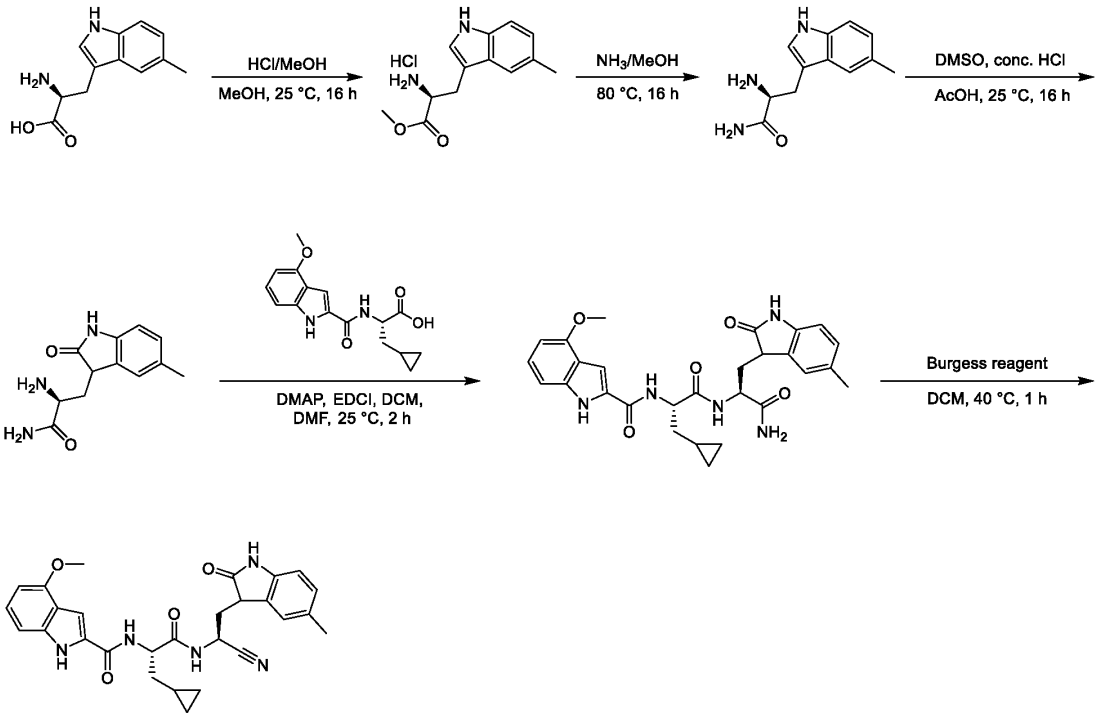
added the water (5 mL) and stirred for 20 min. Then the reaction mixture was concentrated to get the crude product. The crude product was purified by pre-HPLC (column: Waters Xbridge BEH C18 100*25 mm*5 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 30% - 60%,10 min). N-[(1S)-2-[[(1S)-1-cyano-2-(4-methyl-2-oxo-indolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo- ethyl]-4-methoxy-1H-indole-2-carboxamide (55 mg, 110.10 umol, 43.83% yield) was obtained as white solid. MS (ESI) *m/z* 500.2 $[M+H]^+$

Step 6: N-[2-[[(1S)-1-cyano-2-(4-methyl-2-oxo-indolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000178] The product was separated by SFC (column: DAICEL CHIRALPAK AD (250 mm*30 mm, 10 um); mobile phase: [0.1% $NH_3.H_2O$ EtOH]; B%: 55%-55%, 20 min). Isomer 1: N-[2-[[(1S)-1-cyano-2-(4-methyl-2-oxo-indolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (10.8 mg, 21.34 umol, 19.38% yield, 98.7% purity) was obtained as the white solid. MS (ESI) *m/z* 500.2 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.57 (s, 1 H) 10.41 - 10.59 (m, 1 H) 8.95 (m, 1 H) 8.42 - 8.59 (m, 1 H) 7.36 (m, 1 H) 7.05 - 7.14 (m, 2 H) 6.99 (br d, *J* = 8.33 Hz, 1 H) 6.73 - 6.82 (m, 1 H) 6.66 (m, 1 H) 6.50 (d, *J* = 7.89 Hz, 1 H) 4.99 - 5.14 (m, 1 H) 4.38 - 4.54 (m, 1 H) 3.88 (s, 3 H) 3.50 - 3.65 (m, 1 H) 3.50 - 3.65 (m, 1 H) 2.62 - 2.72 (m, 1 H) 2.28 (d, *J* = 12.93 Hz, 2 H) 2.17 (m, 1 H) 1.92 - 2.04 (m, 1 H) 1.71 - 1.87 (m, 1 H) 1.43 - 1.61 (m, 2 H) 0.73 - 0.88 (m, 1 H) 0.33 - 0.49 (m, 2 H) 0.02 - 0.25 (m, 2 H)

[000179] Isomer 2: N-[2-[[(1S)-1-cyano-2-(4-methyl-2-oxo-indolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (17.2 mg, 34.29 umol, 31.15% yield, 99.6% purity) was obtained as the white solid.. MS (ESI) *m/z* 500.2 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.55 (br d, *J* = 1.53 Hz, 1 H) 10.40 - 10.54 (m, 1 H) 8.93 (m, 1 H) 8.48 (m, 1 H) 7.34 (m, 1 H) 7.03 - 7.14 (m, 2 H) 6.98 (br d, *J* = 8.11 Hz, 1 H) 6.71 - 6.79 (m, 1 H) 6.64 (m, 1 H) 6.45 - 6.52 (m, 1 H) 4.97 - 5.10 (m, 1 H) 4.36 - 4.53 (m, 1 H) 3.86 (s, 3 H) 3.49 - 3.64 (m, 1 H) 2.57 - 2.64 (m, 1 H) 2.26 (d, *J* = 12.94 Hz, 3 H) 2.16 (m, 1 H) 1.96 (m, 1 H) 1.70 - 1.84 (m, 1 H) 1.44 - 1.57 (m, 1 H) 0.77 (m, 1 H) 0.34 - 0.44 (m, 2 H) 0.04 - 0.22 (m, 2 H)

Example 264. Synthesis of viral protease inhibitor compound 1085



Step 1: methyl (2S)-2-amino-3-(5-methyl-1H-indol-3-yl)propanoate

[000180] A mixture of (2S)-2-amino-3-(5-methyl-1H-indol-3-yl)propanoic acid (1 g, 4.58 mmol, 1 *eq*) in HCl/MeOH (4 M, 20 mL) was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-amino-3-(5-methyl-1H-indol-3-yl)propanoate (1.1 g, 4.09 mmol, 89.33% yield, HCl) as a yellow solid.

Step 2: (2S)-2-amino-3-(5-methyl-1H-indol-3-yl)propanamide

[000181] A mixture of methyl (2S)-2-amino-3-(5-methyl-1H-indol-3-yl)propanoate (1.1 g, 4.74 mmol, 1 *eq*) in NH_3/MeOH (7 M, 34.71 mL, 51.30 *eq*) was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (2S)-2-amino-3-(5-methyl-1H-indol-3-yl)propanamide (1 g, 4.60 mmol, 97.19% yield) as a yellow solid. MS (ESI) *m/z* 218.1 $[M+H]^+$

Step 3: (2S)-2-amino-3-(5-methyl-2-oxo-indolin-3-yl)propanamide

[000182] A mixture of DMSO (539.43 mg, 6.90 mmol, 539.43 uL, 1.5 *eq*) and HCl (12 M, 1.53 mL, 4 *eq*) was added to a mixture of (2S)-2-amino-3-(5-methyl-1H-indol-3-yl)propanamide (1 g, 4.60 mmol, 1 *eq*) in AcOH (10 mL), the mixture was stirred at

25 °C for 16 h. Upon completion, the reaction mixture was purified by prep-HPLC (HCl condition; column: Welch Xtimate C18 100*25mm*3um;mobile phase: [water(0.04%HCl)-ACN];B%: 1%-10%,8min) to give (2S)-2-amino-3-(5-methyl-2-oxo-indolin-3-yl)propanamide (370 mg, 682.05 umol, 14.82% yield, 43% purity) as a yellow solid. MS (ESI) *m/z* 234.0 $[M+H]^+$

Step 4: N-[(1S)-2-[[(1S)-2-amino-1-[(5-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

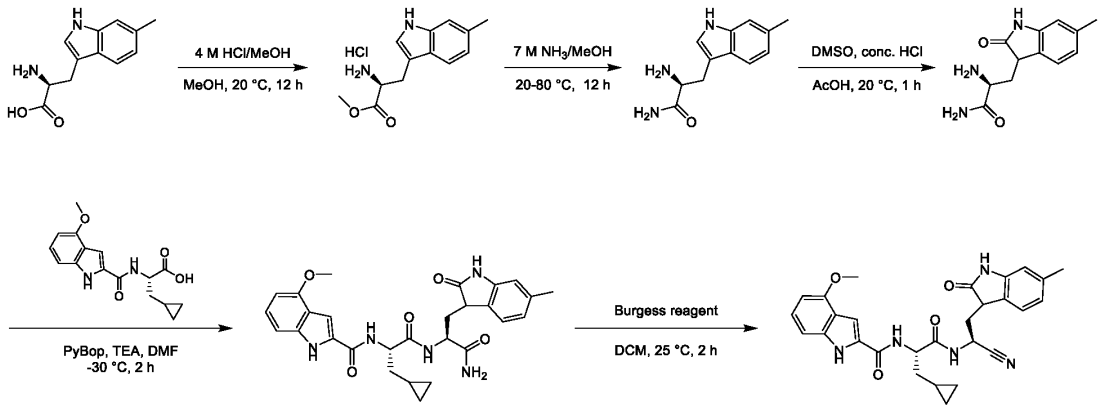
[000183] To a solution of (2S)-2-amino-3-(5-methyl-2-oxo-indolin-3-yl)propanamide (370 mg, 682.05 umol, 43% purity, 1 *eq*) and (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (226.82 mg, 750.26 umol, 1.1 *eq*) in DCM (5 mL) and DMF (2 mL) was added DMAP (249.98 mg, 2.05 mmol, 3 *eq*) and EDCI (261.50 mg, 1.36 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O 10 mL and extracted with EA 18 mL (6 mL * 3). The combined organic layers were washed with brine 9 mL (9 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by prep-TLC (SiO_2, EA:MeOH = 10:1) to give N-[(1S)-2-[[(1S)-2-amino-1-[(5-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (150 mg, 289.81 umol, 42.49% yield) as a white solid. MS (ESI) *m/z* 518.2 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-1-cyano-2-(5-methyl-2-oxo-indolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000184] A mixture of N-[(1S)-2-[[(1S)-2-amino-1-[(5-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (120 mg, 185.48 umol, 80% purity, 1 *eq*) in DCM (2 mL) was added Burgess reagent (88.40 mg, 370.96 umol, 2 *eq*) in one portion. The mixture was stirred at 40 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min) to give N-[(1S)-2-[[(1S)-1-cyano-2-(5-methyl-2-oxo-indolin-3-

yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (30 mg, 60.05 umol, 32.38% yield) as a white solid. MS (ESI) *m/z* 500.1 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ = 11.62 - 11.48 (m, 1H), 10.47 - 10.30 (m, 1H), 9.12 - 8.89 (m, 1H), 8.58 - 8.45 (m, 1H), 7.37 (br d, *J* = 6.7 Hz, 1H), 7.19 - 7.04 (m, 2H), 7.02 - 6.95 (m, 2H), 6.77 - 6.63 (m, 1H), 6.55 - 6.15 (m, 1H), 5.25 - 5.02 (m, 1H), 4.58 - 4.40 (m, 1H), 3.89 (d, *J* = 3.3 Hz, 3H), 3.51 - 3.38 (m, 1H), 2.32 - 2.13 (m, 5H), 1.87 - 1.70 (m, 1H), 1.59 - 1.39 (m, 1H), 0.80 (br s, 1H), 0.50 - 0.28 (m, 2H), 0.27 - -0.03 (m, 2H)

Example 265. Synthesis of viral protease inhibitor compound 1087



Step 1: methyl (2S)-2-amino-3-(6-methyl-1H-indol-3-yl)propanoate

[000185] To (2S)-2-amino-3-(6-methyl-1H-indol-3-yl)propanoic acid (1.00 g, 4.58 mmol, 1 *eq*) was added HCl/MeOH (4 M, 50.00 mL, 43.65 *eq*) in one portion at 20 °C under N_2. The mixture was stirred at 20 °C for 12 h. Upon completion, the reaction mixture was concentrated to get Methyl (2S)-2-amino-3-(6-methyl-1H-indol-3-yl) propanoate (1.15 g, crude, HCl) as the light yellow solid and used directly next step. MS (ESI) *m/z* 233.1 $[M+H]^+$

Step 2: (2S)-2-amino-3-(6-methyl-1H-indol-3-yl)propanamide

[000186] Methyl (2S)-2-amino-3-(6-methyl-1H-indol-3-yl) propanoate (1.15 g, 4.28 mmol, 1 *eq*, HCl) was dissolved in NH_3/MeOH (7 M, 20 mL, 32.72 *eq*) at 20 °C. The mixture was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was cooled to 20 °C and concentrated to get the product. (2S)-2-amino-3-(6-methyl-1H-

indol-3-yl) propanamide (1.1 g, crude) was obtained as the light yellow solid and used directly next step. MS (ESI) *m/z* 218.1 $[M+H]^+$

Step 3: (2S)-2-amino-3-(6-methyl-2-oxo-indolin-3-yl)propanamide

[000187] To a solution of (2S)-2-amino-3-(6-methyl-1H-indol-3-yl)propanamide (1.08 g, 4.97 mmol, 1 *eq*) in AcOH (10 mL) was added drop wise the solution of DMSO (582.58 mg, 7.46 mmol, 582.58 uL, 1.5 *eq*) and HCl (12 M, 1.66 mL, 4 *eq*) at 20 °C under N_2. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was added the saturated sodium bicarbonate aqueous solution to pH~6. The product was purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*10 um; mobile phase: [water (0.04%HCl) -ACN]; B%: 1%-30%, 10min) to give (2S)-2-amino-3-(6-methyl-2-oxo-indolin-3-yl)propanamide (0.22 g, 754.50 umol, 15.18% yield, 80% purity) as the green solid. MS (ESI) *m/z* 234.1 $[M+H]^+$

Step 4: N-[(1S)-2-[[(1S)-2-amino-1-[(6-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

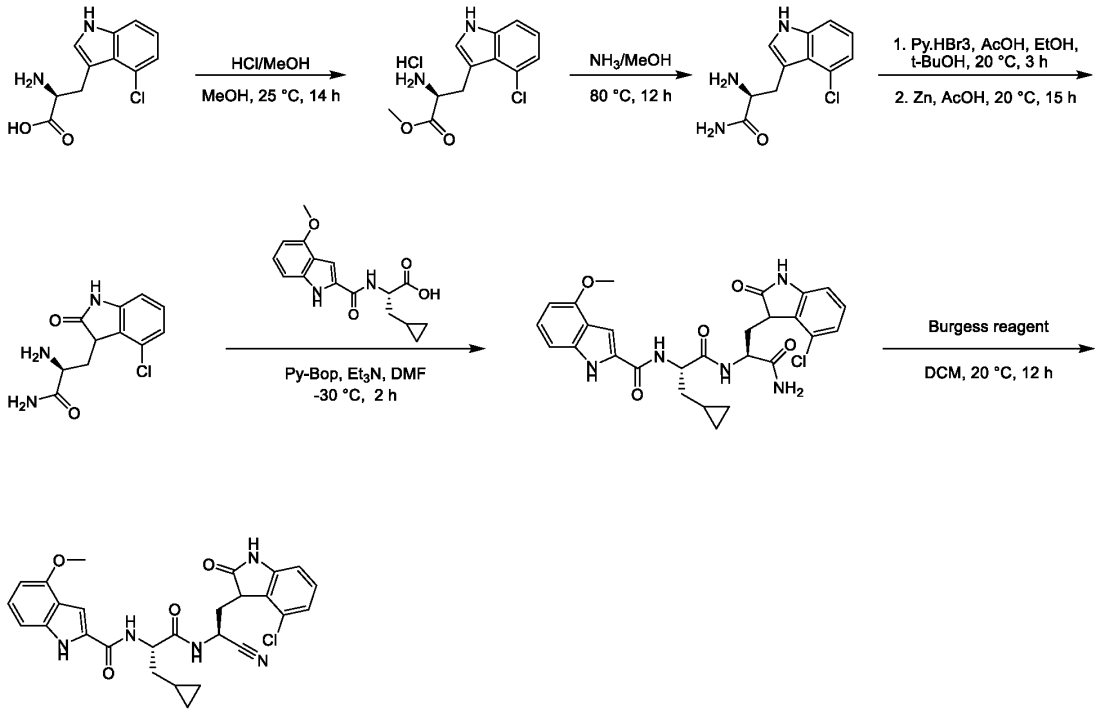
[000188] To a mixture of (2S)-2-amino-3-(6-methyl-2-oxo-indolin-3-yl)propanamide (200.00 mg, 857.39 umol, 1 *eq*) and (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (324.01 mg, 857.39 umol, 80% purity, 1 *eq*) in DMF (0.5 mL) was added PyBop (446.18 mg, 857.39 umol, 1 *eq*) and TEA (260.28 mg, 2.57 mmol, 358.01 uL, 3 *eq*) in one portion at -30 °C under N_2. The mixture was stirred at -30 °C for 2 h. Upon completion, the reaction mixture was quenched by addition water (20 mL) at 20 °C, and then diluted with DCM (20 mL) and extracted with DCM (10 mL * 2). The combined organic layers were concentrated under reduced pressure to give N-[(1S)-2-[[(1S)-2-amino-1-[(6-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (200 mg, crude) as the light yellow oil. MS (ESI) *m/z* 518.2 $[M+H]^+$

Step 5: N-[(1S)-2-[[(1S)-1-cyano-2-(6-methyl-2-oxo-indolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide

[000189] To a mixture of N-[(1S)-2-[[(1S)-2-amino-1-[(6-methyl-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (100 mg, 193.21 umol, 1 *eq*) in DCM (20 mL) was added

Burgess reagent (138.13 mg, 579.63 umol, 3 *eq*) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was added the water (5 mL) and stirred for 20 min. Then the reaction mixture was concentrated to get the crude product. The crude protuct was purified by pre-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-60%, 10min) to give N-[(1S)-2-[[(1S)-1-cyano-2-(6-methyl-2-oxo-indolin-3-yl)ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (2.11 mg, 4.20 umol, 2.17% yield, 99.4% purity) as white solid. MS (ESI) *m/z* 500.2 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ = 11.67 - 11.47 (m, 1H), 10.52 - 10.34 (m, 1H), 9.11 - 8.93 (m, 1H), 8.59 - 8.44 (m, 1H), 7.40 - 7.31 (m, 1H), 7.18 - 7.03 (m, 2H), 7.01 - 6.94 (m, 1H), 6.82 - 6.70 (m, 1H), 6.64 (d, *J* = 7.2 Hz, 1H), 6.54 - 6.45 (m, 1H), 5.19 - 5.01 (m, 1H), 4.53 - 4.41 (m, 1H), 3.91 - 3.83 (m, 3H), 3.49 - 3.36 (m, 1H), 2.31 (br d, *J* = 2.0 Hz, 5H), 1.85 - 1.68 (m, 1H), 1.59 - 1.38 (m, 1H), 0.86 - 0.70 (m, 1H), 0.44 - 0.28 (m, 2H), 0.24 - -0.01 (m, 2H).

Example 266. Synthesis of viral protease inhibitor compound 1091



Step 1: (S)-methyl 2-amino-3-(4-chloro-1H-indol-3-yl)propanoate

[000190] A mixture of (2S)-2-amino-3-(4-chloro-1H-indol-3-yl)propanoic acid (1 g, 4.19 mmol, 1 eq) in HCl/MeOH (4 M, 20 mL, 19.09 eq) was stirred at 25 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the methyl (2S)-2-amino-3-(4-chloro-1H-indol-3-yl)propanoate (1 g, crude) as a yellow solid. MS (ESI) *m/z* 251.1 $[M-H]^+$.

Step 2: (S)-2-amino-3-(4-chloro-1H-indol-3-yl)propanamide

[000191] A solution of methyl (2S)-2-amino-3-(4-chloro-1H-indol-3-yl)propanoate (1 g, 3.96 mmol, 1 eq) in NH_3/MeOH (7 M, 20.00 mL, 35.38 eq) was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the (2S)-2-amino-3-(4-chloro-1H-indol-3-yl)propanamide (0.9 g, crude) as a yellow solid. MS (ESI) *m/z* 238.1 $[M+H]^+$.

Step 3: (2S)-2-amino-3-(4-chloro-2-oxoindolin-3-yl)propanamide

[000192] To a solution of (2S)-2-amino-3-(4-chloro-1H-indol-3-yl)propanamide (500 mg, 2.10 mmol, 1 eq) in t-BuOH (6 mL), EtOH (4 mL) and AcOH (2 mL), then BLAH; pyridin-1-ium (672.78 mg, 2.10 mmol, 1 eq) was added, the mixture was stirred at 20 °C for 3 h, then AcOH (2 mL) and Zn (1.05 g, 15.99 mmol, 7.6 eq) was added, the mixture was stirred at 20 °C for 15 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 80 * 40 mm * 3 um; mobile phase: [water (0.04% HCl) - ACN]; B%: 1% - 25%, 7 min) to give the (2S)-2-amino-3-(4-chloro-2-oxo-indolin-3-yl)propanamide (35 mg, 137.97 umol, 6.56% yield) was obtained as a white solid. MS (ESI) *m/z* 254.1 $[M+H]^+$.

Step 4: N-((2S)-1-(((2S)-1-amino-3-(4-chloro-2-oxoindolin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

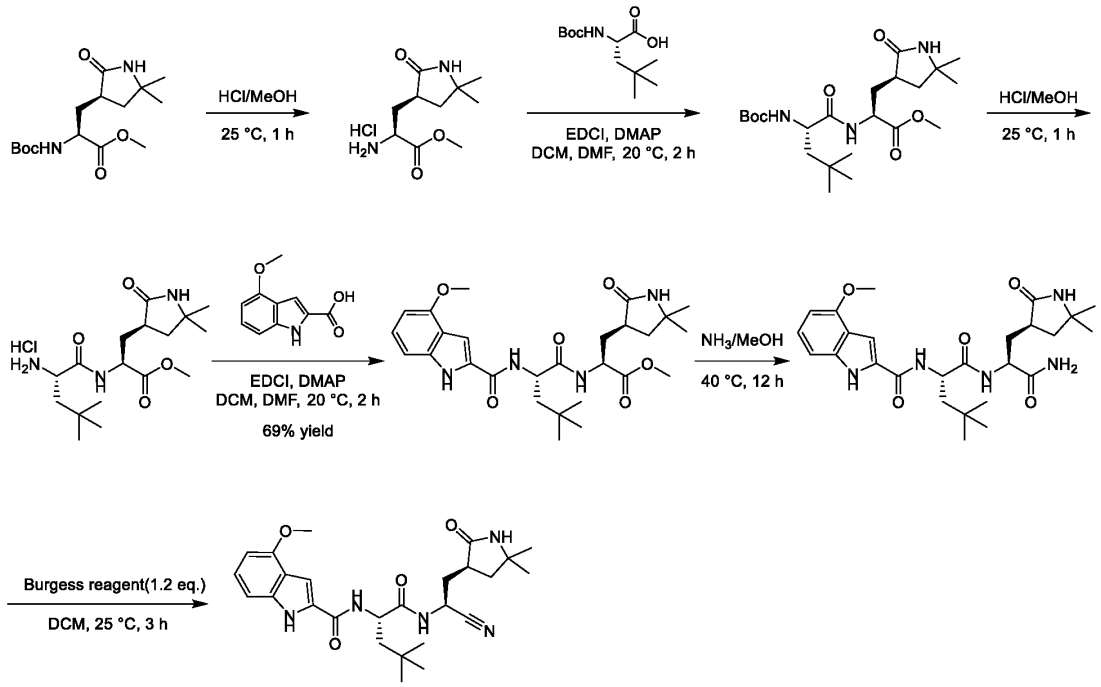
[000193] To a solution of (2S)-2-amino-3-(4-chloro-2-oxo-indolin-3-yl)propanamide (30 mg, 103.40 umol, 1 eq, HCl) and (2S)-3-cyclopropyl-2-[(4-methoxy-1H-indole-2-carbonyl)amino]propanoic acid (40.64 mg, 134.42 umol, 1.3 eq) in DMF (1 mL) was added Py-Bop (53.81 mg, 103.40 umol, 1 eq) was cooled to -30 °C, then Et_3N (31.39 mg, 310.19 umol, 43.17 uL, 3 eq) in DMF (0.5 mL) was added drop-wise, the mixture was stirred at -30 °C for 2 h. Upon completion, the reaction mixture was quenched by

addition H_2O 20 mL at 0 °C, and then extracted with DCM (10 mL * 3). The combined organic layers were washed with brine 15 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, EtOAc:MeOH = 20:1) to give the N-[(1S)-2-[[(1S)-2-amino-1-[(4-chloro-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (35 mg, 65.06 umol, 62.92% yield) was obtained as a white solid. MS (ESI) *m/z* 538.2 $[M+H]^+$.

Step 5: N-((2S)-1-(((1S)-2-(4-chloro-2-oxoindolin-3-yl)-1-cyanoethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000194] To a sloution of N-[(1S)-2-[[(1S)-2-amino-1-[(4-chloro-2-oxo-indolin-3-yl)methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (35 mg, 65.06 umol, 1 eq) in DCM (2 mL) was added burgess reagent (31.01 mg, 130.11 umol, 2 eq), then the mixture was stirrred at 20 °C for 12 h. Upon completion, the reaction mixture was quenched by addition H_2O 0.5 mL, concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 * 30mm * 3um; mobile phase: [water (0.2% FA) - ACN]; B%: 30% - 60%, 8 min) to give the N-[(1S)-2-[[(1S)-2-(4-chloro-2-oxo-indolin-3-yl)-1-cyano-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4-methoxy-1H-indole-2-carboxamide (4 mg, 7.69 umol, 11.82% yield, 100% purity) was obtained as a yellow solid. MS (ESI) *m/z* 520.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.29 - 7.23 (m, 1H), 7.21 - 7.10 (m, 2H), 7.07 - 6.95 (m, 2H), 6.88 - 6.65 (m, 1H), 6.55 - 6.49 (m, 1H), 5.28 - 4.53 (m, 1H), 3.93 (d, *J* = 2.6 Hz, 3H), 3.85 - 3.72 (m, 1H), 3.01 - 2.85 (m, 1H), 2.62 - 2.28 (m, 1H), 1.88 - 1.78 (m, 1H), 1.70 - 1.55 (m, 1H), 1.41 - 1.26 (m, 1H), 0.95 - 0.76 (m, 1H), 0.58 - 0.39 (m, 2H), 0.27 - 0.09 (m, 2H).

Example 267. Synthesis of viral protease inhibitor compound 1101



Step 1: (S)-methyl 2-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000195] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-(5,5-dimethyl-2-oxo-pyrrolidin-3-yl)propanoate (500.00 mg, 1.59 mmol, 1 eq) in HCl/MeOH (4 M, 10.00 mL, 25.15 eq) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-amino-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (390 mg, crude, HCl) as a white solid.

Step 2: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000196] To a solution of methyl (2S)-2-amino-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (390 mg, 1.82 mmol, 1 eq) and (2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (580.48 mg, 2.37 mmol, 1.3 eq) in DCM (10 mL) and DMF (3 mL) was added DMAP (667.11 mg, 5.46 mmol, 3 eq) and EDCI (697.88 mg, 3.64 mmol, 2 eq), and then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 30 mL at 0 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a

residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 5:1 to 0:1) to give the product methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (510 mg, 924.00 umol, 50.76% yield, 80% purity) as a white solid. MS (ESI) *m/z* 442.2 $[M+H]^+$.

Step 3: (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000197] To a solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (250 mg, 566.17 umol, 1 eq) in HCl/MeOH (4 M, 5 mL, 35.32 eq), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (190 mg, crude, HCl) as a white solid.

Step 4: (S)-methyl 3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((S)-2-(4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)propanoate

[000198] To a solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (190 mg, 502.77 umol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (124.96 mg, 653.60 umol, 1.3 eq) in DCM (4 mL) and DMF (1 mL), and then DMAP (184.27 mg, 1.51 mmol, 3 eq) and EDCI (192.76 mg, 1.01 mmol, 2 eq) was added, then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give the product methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]propanoate (200 mg, 349.78 umol, 69.57% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 515.2 $[M+H]^+$.

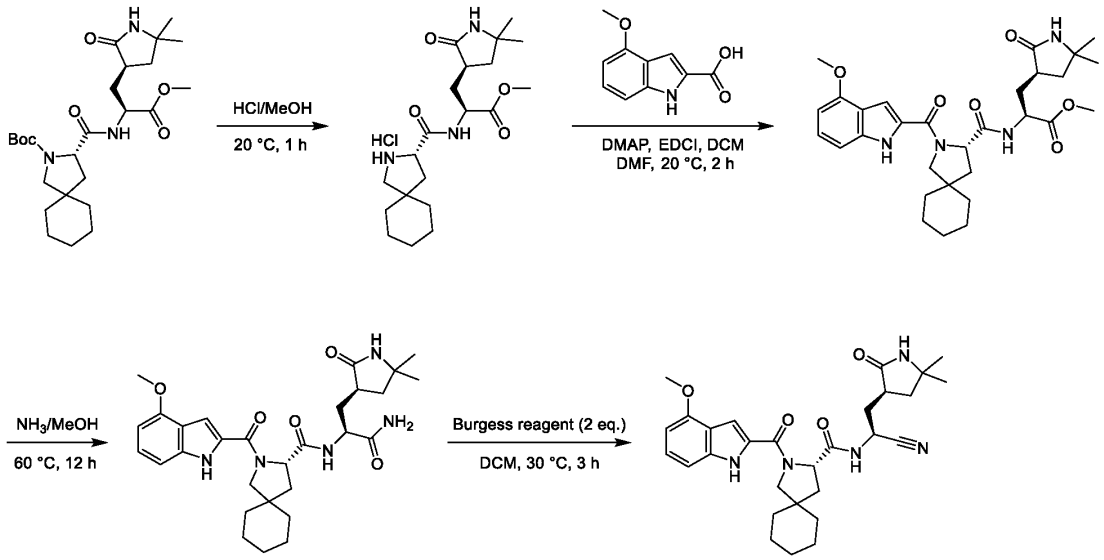
Step 5: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000199] A solution of methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[(2S)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]propanoate (200 mg, 388.64 umol, 1 eq) in NH_3/MeOH (7 M, 5 mL, 90.06 eq) was stirred at 40 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product N-[(1S)-1-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (190 mg, crude) as a white solid. MS (ESI) *m/z* 500.2 $[M+H]^+$.

Step 6: N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000200] To a solution of N-[(1S)-1-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (160 mg, 320.26 umol, 1 eq) in DCM (3 mL) and burgess reagent (91.58 mg, 384.31 umol, 1.2 eq) was added, and then the mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xtimate C18 10 u 250 mm * 80 mm; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%:25% - 55%, 35 min) to give the product N-[(1S)-1-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (67.35 mg, 139.85 umol, 43.67% yield, 100% purity) as a white solid. MS (ESI) *m/z* 482.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.54 (d, J = 1.6 Hz, 1H), 8.87 (d, J = 8.2 Hz, 1H), 8.46 (d, J = 8.1 Hz, 1H), 7.81 (s, 1H), 7.33 (d, J = 1.5 Hz, 1H), 7.12 - 7.06 (m, 1H), 7.03 - 6.98 (m, 1H), 6.50 (d, J = 7.6 Hz, 1H), 4.98 - 4.89 (m, 1H), 4.51 (dt, J = 3.6, 8.5 Hz, 1H), 3.88 (s, 3H), 2.60 - 2.54 (m, 1H), 2.17 (dt, J = 4.8, 9.0 Hz, 1H), 1.95 (dd, J = 8.6, 12.2 Hz, 1H), 1.83 - 1.72 (m, 2H), 1.71 - 1.63 (m, 1H), 1.49 (t, J = 11.6 Hz, 1H), 1.14 (s, 3H), 1.02 (s, 3H), 0.93 (s, 9H)

Example 268. Synthesis of viral protease inhibitor compound 1103



Step 1: (S)-methyl 3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((S)-2-azaspiro[4.5]decane-3-carboxamido)propanoate hydrochloride

[000201] A solution of tert-butyl (3S)-3-[[(1S)-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (400 mg, 834.01 umol, 1 eq) in HCl/MeOH (4 M, 5 mL, 23.98 eq) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-[[(3S)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (340 mg, crude, HCl) as a white solid.

Step 2: (S)-methyl 3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((S)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)propanoate

[000202] To a solution of 4-methoxy-1H-indole-2-carboxylic acid (170.98 mg, 894.33 umol, 1.2 eq) and methyl (2S)-2-[[(3S)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (310 mg, 745.28 umol, 1 eq, HCl) in DCM (15 mL) and DMF (3 mL) was added DMAP (273.15 mg, 2.24 mmol, 3 eq) and EDCI (285.74 mg, 1.49 mmol, 2 eq), then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (50 mL) at 0 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column

chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 0/1) to give the product methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[(3S)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]propanoate (320 mg, 561.65 umol, 75.36% yield, 97% purity) as a yellow solid. MS (ESI) *m/z* 553.2 $[M+H]^+$.

Step 3: (S)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

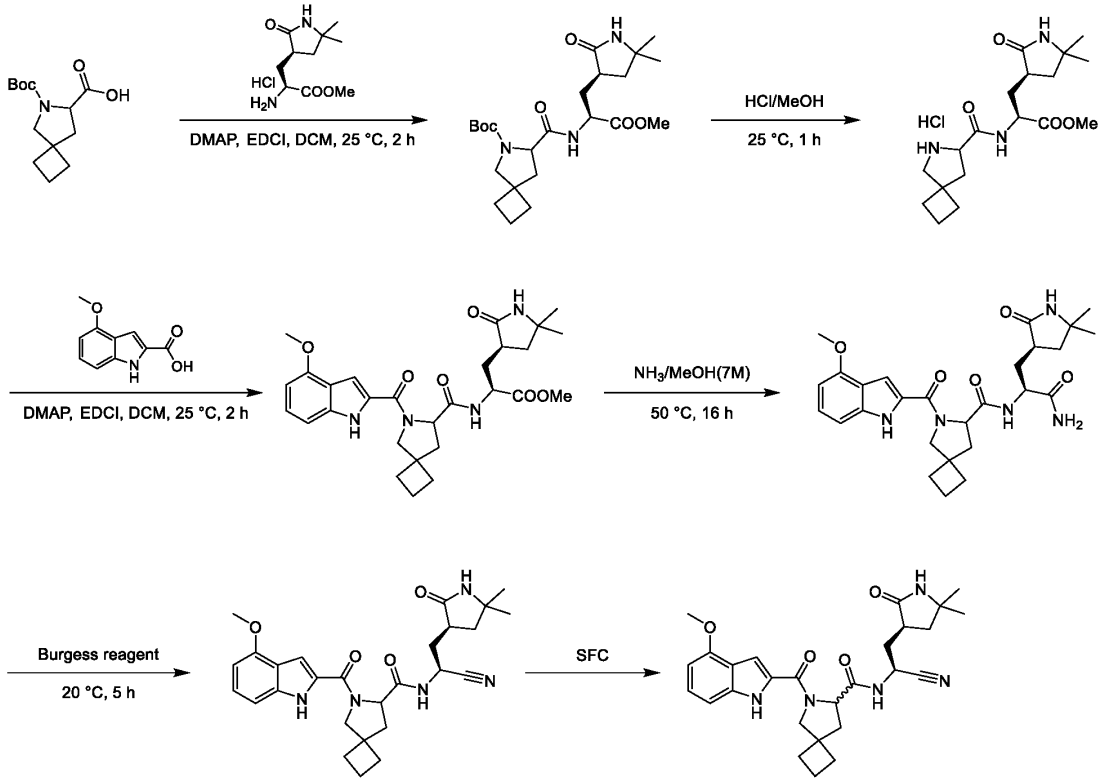
[000203] To a solution of methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[(3S)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]propanoate (320 mg, 579.02 umol, 1 eq) in NH_3/MeOH (7 M, 5.00 mL, 60.45 eq) was stirred at 60 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (310 mg, crude) as a yellow solid. MS (ESI) *m/z* 538.3 $[M+H]^+$.

Step 4: (S)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000204] A solution of (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (310 mg, 501.63 umol, 87% purity, 1 eq) and burgess reagent (239.09 mg, 1.00 mmol, 2 eq) in DCM (5 mL) was stirred at 30 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30 mm * 10 um; mobile phase: [water(10 mM NH_4HCO_3) - ACN]; B%: 35% - 65%, 8 min) to give the product (3S)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (115.37 mg, 222.02 umol, 44.26% yield, 100% purity) as a white solid. MS (ESI) *m/z* 520.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.53 (s, 1H), 8.89 (d, *J* = 8.1 Hz, 1H), 7.81 (s, 1H), 7.15 - 7.08 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 1.2 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 4.96 - 4.89 (m, 1H), 4.50 (t, *J* = 8.5 Hz, 1H), 3.89 (s, 3H), 3.87 - 3.79 (m, 1H), 3.67 (d, *J* = 10.4 Hz, 1H), 2.26 - 2.11 (m, 2H), 2.00 (dd,

J = 8.4, 12.0 Hz, 1H), 1.78 - 1.70 (m, 1H), 1.63 - 1.31 (m, 13H), 1.14 (s, 3H), 1.08 - 1.00 (m, 3H).

Example 269. Synthesis of viral protease inhibitor compound 1105



Step 1: tert-butyl 7-[[(1S)-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate

[000205] To a mixture of methyl (2S)-2-amino-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (450 mg, 2.10 mmol, 1 *eq*) and 6-tert-butoxycarbonyl-6-azaspiro[3.4]octane-7-carboxylic acid (589.83 mg, 2.31 mmol, 1.1 *eq*) in DCM (10 mL), was added DMAP (769.75 mg, 6.30 mmol, 3 *eq*) and EDCI (805.24 mg, 4.20 mmol, 2 *eq*), the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O 25 mL and extracted with DCM 45 mL (15 mL * 3). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 0/1) to give tert-butyl 7-[[(1S)-1-[[(3R)-5,5-dimethyl-2-oxo-

pyrrolidin-3-yl]methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (0.9 g, 1.79 mmol, 85.41% yield, 90% purity) as a yellow solid. MS (ESI) *m/z* 452.3 $[M+H]^+$

Step2: methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[000206] A mixture of tert-butyl 7-[[(1S)-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-6-azaspiro[3.4]octane-6-carboxylate (0.9 g, 1.79 mmol, 90% purity, 1 *eq*) in HCl/MeOH (4M, 15 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (800 mg, crude, HCl) as a white solid.

Step 3: methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]propanoate

[000207] A mixture of methyl (2S)-2-(6-azaspiro[3.4]octane-7-carbonylamino)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (386.00 mg, 995.10 umol, 1 *eq*, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (199.76 mg, 1.04 mmol, 1.05 *eq*) in DCM (10 mL) was added DMAP (364.71 mg, 2.99 mmol, 3 *eq*) and EDCI (381.53 mg, 1.99 mmol, 2 *eq*), and then the mixture was stirred at 25 °C for 2 h under N_2 atmosphere. Upon completion, the reaction mixture was diluted with H_2O 20 mL and extracted with EA 45 mL (15 mL * 3). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 0/1) to give methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]propanoate (390 mg, 691.37 umol, 69.48% yield, 93% purity) as a yellow solid. MS (ESI) *m/z* 525.3 $[M+H]^+$

Step 4: N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000208] A mixture of methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carbonyl]amino]propanoate (370 mg, 705.29 umol, 1 *eq*) in NH_3/MeOH(7 M, 15 mL, 148.88 *eq*) was stirred at

50 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (320 mg, 571.43 umol, 81.02% yield, 91% purity) as a yellow solid. MS (ESI) *m/z* 510.3 $[M+H]^+$

Step 5: N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide

[000209] A mixture of N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide (320 mg, 571.43 umol, 91% purity, 1 *eq*) in DCM (10 mL) was added Burgess reagent (272.36 mg, 1.14 mmol, 2 *eq*), and the resulting mixture was stirred at 20 °C for 5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (neutral condition;column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min) to give desired compound 200 mg as a white solid, which was further separated by SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O IPA];B%: 52%-52%,12min) to give N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 1 (90 mg, 181.62 umol, 31.78% yield, 99.2% purity) as a white solid. MS (ESI) *m/z* 492.1 $[M+H]^+$

[000210] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.55 (s, 1H), 8.83 (d, *J* = 8.2 Hz, 1H), 7.82 (s, 1H), 7.16 - 7.07 (m, 1H), 7.05 - 6.94 (m, 2H), 6.52 (d, *J* = 7.7 Hz, 1H), 4.93 (q, *J* = 8.1 Hz, 1H), 4.45 (t, *J* = 7.4 Hz, 1H), 4.04 - 3.69 (m, 5H), 2.70 - 2.56 (m, 1H), 2.35 - 2.25 (m, 1H), 2.21 - 1.69 (m, 10H), 1.50 (br t, *J* = 11.5 Hz, 1H), 1.20 - 0.85 (m, 6H).

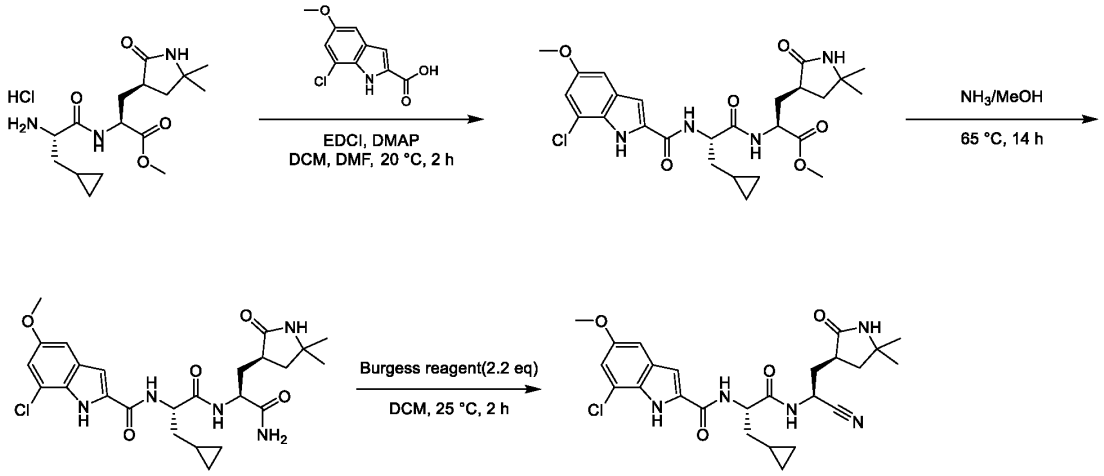
[000211] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ = 11.39 - 11.15 (m, 1H), 8.83 - 8.51 (m, 1H), 7.66 - 7.53 (m, 1H), 7.17 - 7.02 (m, 2H), 7.01 - 6.88 (m, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 4.99 - 4.86 (m, 1H), 4.64 - 4.44 (m, 1H), 4.05 - 3.82 (m, 5H), 2.54 (br s, 1H), 2.39 - 2.25 (m, 1H), 2.20 - 1.73 (m, 10H), 1.61 - 1.42 (m, 1H), 1.23 - 1.03 (m, 6H).

[000212] To give N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-6-(4-methoxy-1H-indole-2-carbonyl)-6-azaspiro[3.4]octane-7-carboxamide Isomer 2 (100 mg, 203.43 umol, 35.60% yield, 100% purity) as a white solid. MS (ESI) *m/z* 492.1 $[M+H]^+$

[000213] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.69 - 11.46 (s, 1H), 8.74 (d, *J* = 8.2 Hz, 1H), 7.87 - 7.66 (m, 1H), 7.17 - 7.09 (m, 1H), 7.06 - 6.95 (m, 2H), 6.60 - 6.40 (m, 1H), 5.00 - 4.74 (m, 1H), 4.45 (t, *J* = 7.2 Hz, 1H), 3.98 (q, *J* = 10.1 Hz, 2H), 3.93 - 3.77 (m, 3H), 2.49 - 2.41 (m, 1H), 2.28 (br dd, *J* = 8.0, 12.2 Hz, 1H), 2.14 (br dd, *J* = 4.0, 9.3 Hz, 2H), 2.05 - 1.80 (m, 7H), 1.80 - 1.67 (m, 1H), 1.50 (br t, *J* = 11.5 Hz, 1H), 1.20 - 1.02 (m, 6H).

[000214] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ = 11.35 - 11.25 (m, 1H), 8.59 (br d, *J* = 5.5 Hz, 1H), 7.56 (br s, 1H), 7.18 - 7.03 (m, 2H), 7.02 - 6.89 (m, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 4.98 - 4.88 (m, 1H), 4.63 - 4.49 (m, 1H), 4.02 - 3.88 (m, 5H), 2.49 - 2.42 (m, 1H), 2.36 - 2.26 (m, 1H), 2.21 - 2.10 (m, 2H), 2.08 - 1.85 (m, 8H), 1.58 - 1.46 (m, 1H), 1.25 - 1.01 (m, 6H).

Example 270. Synthesis of viral protease inhibitor compound 1115



Step 1: (S)-methyl 2-((S)-2-(7-chloro-5-methoxy-1H-indole-2-carboxamido)-3 cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000215] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (150 mg,

414.52 umol, 1 *eq*, HCl) and 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (140.29 mg, 621.78 umol, 1.5 *eq*) in DCM (4 mL) was added DMAP (101.28 mg, 829.04 umol, 2 *eq*) and EDCI (119.20 mg, 621.78 umol, 1.5 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 40 mL, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give methyl (2S)-2-[[(2S)-2-[(7-chloro-5-methoxy-1H-indole-2-carbonyl) amino]-3-cyclopropyl-propanoyl] amino]-3-[(3R)-5, 5-dimethyl-2-oxo-pyrrolidin-3-yl] propanoate (198 mg, 360.33 umol, 86.93% yield, 97% purity) as a yellow solid. MS (ESI) *m/z* 532.2 $[M+H]^+$.

Step 2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-5-methoxy-1H-indole-2-carboxamide.

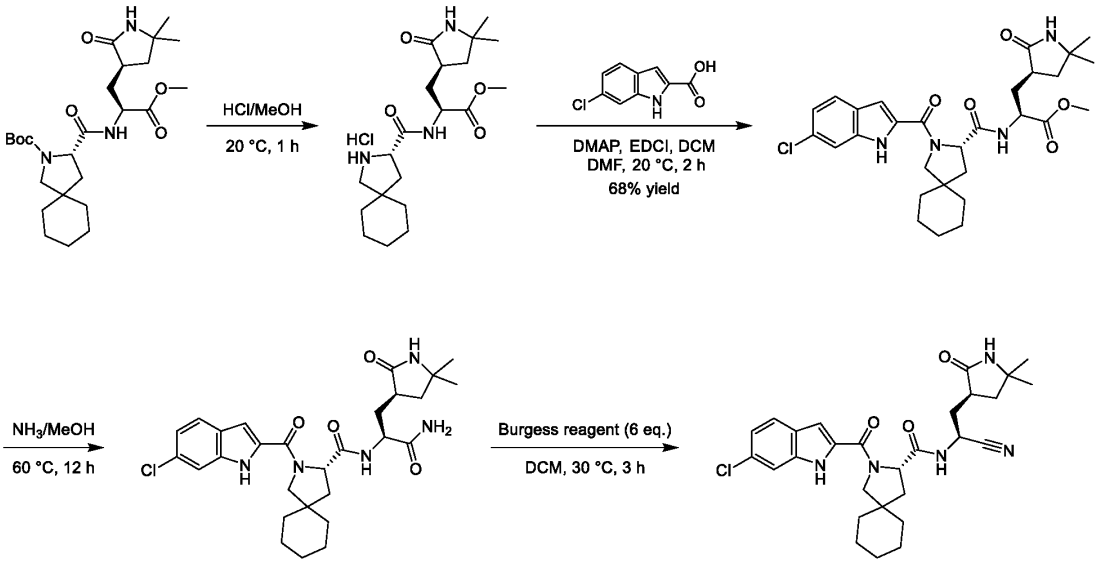
[000216] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-5-methoxy-1H-indole-2-carbonyl) amino]-3-cyclopropyl-propanoyl] amino]-3-[(3R)-5, 5-dimethyl-2-oxo-pyrrolidin-3-yl] propanoate (160 mg, 300.18 umol, 1 *eq*) in NH_3MeOH (7 M, 10 mL, 233.19 *eq*) was stirred at 65 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give crude product N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1 (cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-5-methoxy-1H-indole-2-carboxamide (166.1 mg, crude) as a yellow solid. MS (ESI) *m/z* 517.2 $[M+H]^+$.

Step 3: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-methoxy-1H-indole-2-carboxamide.

[000217] A solution of N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-5-methoxy-1H-indole-2-carboxamide (140 mg, 270.27 umol, 1 *eq*) in DCM (4 mL) was added burgess reagent (141.69 mg, 594.59 umol, 2.2 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was remove DCM under N_2. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-60%, 8min) to give 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-

pyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-methoxy-1H-indole-2-carboxamide (45 mg, 90.00 umol, 33.30% yield, 100% purity) as a white solid. MS (ESI) *m/z* 499.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.67 - 11.34 (m, 1H), 9.06 - 8.96 (m, 1H), 8.69 - 8.62 (m, 1H), 7.90 - 7.79 (m, 1H), 7.19 - 7.11 (m, 2H), 7.02 - 6.96 (m, 1H), 5.02 - 4.92 (m, 1H), 4.57 - 4.45 (m, 1H), 3.82 - 3.73 (m, 3H), 2.63 - 2.54 (m, 1H), 2.26 - 2.12 (m, 1H), 2.03 - 1.95 (m, 1H), 1.86 - 1.73 (m, 2H), 1.58 - 1.44 (m, 2H), 1.16 - 1.12 (m, 3H), 1.09 - 1.05 (m, 3H), 0.85 - 0.77 (m, 1H), 0.51 - 0.38 (m, 2H), 0.26 - 0.16 (m, 1H), 0.14 - 0.06 (m, 1H).

Example 271. Synthesis of viral protease inhibitor compound 1119



Step 1: (S)-methyl 3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((S)-2-azaspiro[4.5]decane-3-carboxamido)propanoate hydrochloride

[000218] To a solution of tert-butyl (3S)-3-[[(1S)-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (400 mg, 834.01 umol, 1 eq) in HCl/MeOH (4 M, 5.00 mL, 23.98 eq), and the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-[[(3S)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (340 mg, crude, HCl) as a white solid.

Step 2: (S)-methyl 2-((S)-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000219] To a solution of methyl (2S)-2-[[(3S)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (310 mg, 745.28 umol, 1 eq, HCl) and 6-chloro-1H-indole-2-carboxylic acid (174.93 mg, 894.33 umol, 1.2 eq) in DCM (10 mL) and DMF (3 mL), and then DMAP (273.15 mg, 2.24 mmol, 3 eq) and EDCI (285.74 mg, 1.49 mmol, 2 eq) was added, then the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H2O 30 mL at 0 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 5:1 to 0:1) to gieve the product (2S)-2-[[(3S)-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (420 mg, 467.44 umol, 62.72% yield, 62% purity) as a yellow solid. MS (ESI) *m/z* 557.2 $[M+H]^+$.

Step 3: (S)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

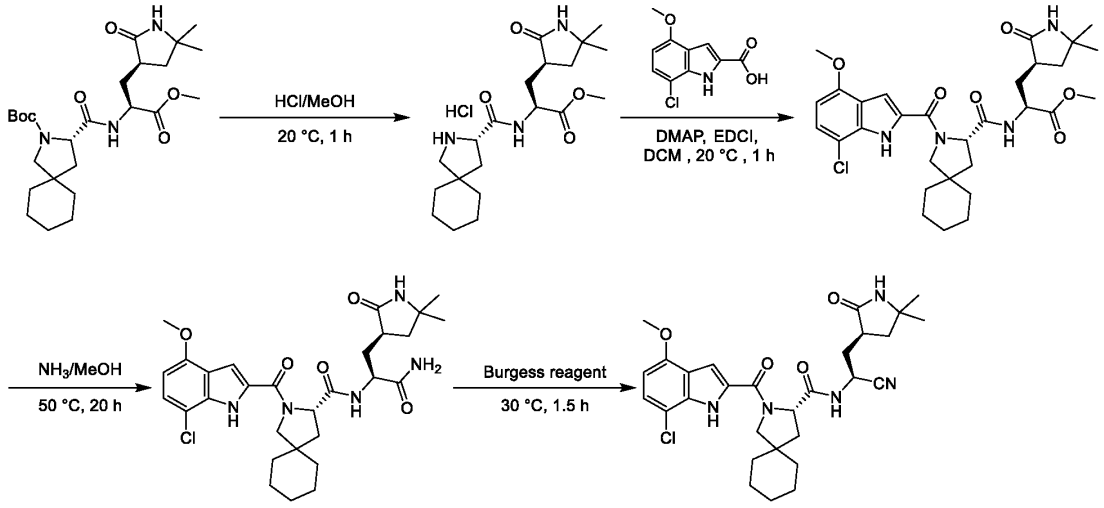
[000220] To a solution of methyl (2S)-2-[[(3S)-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (420 mg, 753.93 umol, 1 eq) in NH_3/MeOH (7 M, 5 mL, 46.42 eq), and the mixture was stirred at 60 °C for 12 h. Upon completion the reaction mixture was concentrated under reduced pressure to give the product (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (400 mg, crude) as a yellow solid. MS (ESI) *m/z* 542.2 $[M+H]^+$.

Step 4: (S)-2-(6-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[000221] To a solution of (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(6-chloro-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (400 mg, 553.44 umol, 75% purity, 1 eq) in DCM (5 mL) was added

burgess reagent (791.32 mg, 3.32 mmol, 6 eq), and then the mixture was stirred at 30 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 45%-75%, 8 min) to give the product (3S)-2-(6-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (80.38 mg, 153.38 umol, 27.71% yield, 99.7% purity) as a white solid. MS (ESI) *m/z* 524.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.62 (d, J = 8.5 Hz, 1H), 7.45 (s, 1H), 7.09 - 6.99 (m, 2H), 5.06 - 4.94 (m, 1H), 4.61 (dd, J = 7.7, 9.8 Hz, 1H), 3.99 (br d, J = 10.2 Hz, 1H), 3.72 (d, J = 10.3 Hz, 1H), 2.97 (br dd, J = 5.0, 8.7 Hz, 1H), 2.51 - 2.34 (m, 1H), 2.30 (br dd, J = 7.7, 12.3 Hz, 1H), 2.16 (dd, J = 8.5, 12.3 Hz, 1H), 1.91 - 1.81 (m, 1H), 1.74 (dd, J = 10.2, 12.4 Hz, 1H), 1.67 - 1.37 (m, 11H), 1.22 (s, 3H), 1.13 - 0.80 (m, 3H).

Example 272. Synthesis of viral protease inhibitor compound 1121



Step 1: (S)-methyl3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((S)-2-azaspiro[4.5]decane-3-carboxamido)propanoate

[000222] A solution of (*S*)-*tert*-butyl3-(((*S*)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-methoxy-1- oxopropan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate (350 mg, 729.76 umol, 1 *eq*) in HCl/MeOH (4 M,4 mL) was stirred at 20 °C for 1 h. Upon the reaction completion, the reaction mixture was concentrated in vacuum to obtained

(*S*)-methyl 3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((*S*)-2-azaspiro[4.5]decane-3-carboxamido)propanoate (280 mg, crude) as a white solid. MS (ESI) *m/z* 380.2 $[M+H]^+$

Step 2: (S)-methyl2-((S)-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000223] To a solution of (*S*)-methyl 3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((*S*)-2-azaspiro[4.5]decane-3-carboxamido)propanoate (280 mg, 673.15 umol, 1 *eq*, HCl) in DCM (2 mL) was added 7-chloro-4-methoxy-1*H*-indole-2-carboxylic acid (182.26 mg, 807.78 umol, 1.2 *eq*), DMAP (205.60 mg, 1.68 mmol, 2.5 *eq*) and EDCI (258.09 mg, 1.35 mmol, 2 *eq*), the mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the reaction mixture was quenched by addition of water (5 mL), and then extracted with DCM (2 mL * 3). The combined organic layers were washed with HCl (1M, 3 mL), then was adjusted pH~7 with sat.$NaHCO_3$ (2 mL), dried over Na_2SO_4, filtered and concentrated in vacuum and was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to obtained (*S*)-methyl 2-((*S*)-2-(7-chloro-4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (300 mg, 510.98 umol, 75.91% yield) as a yellow solid. MS (ESI) *m/z* 587.3 $[M+H]^+$

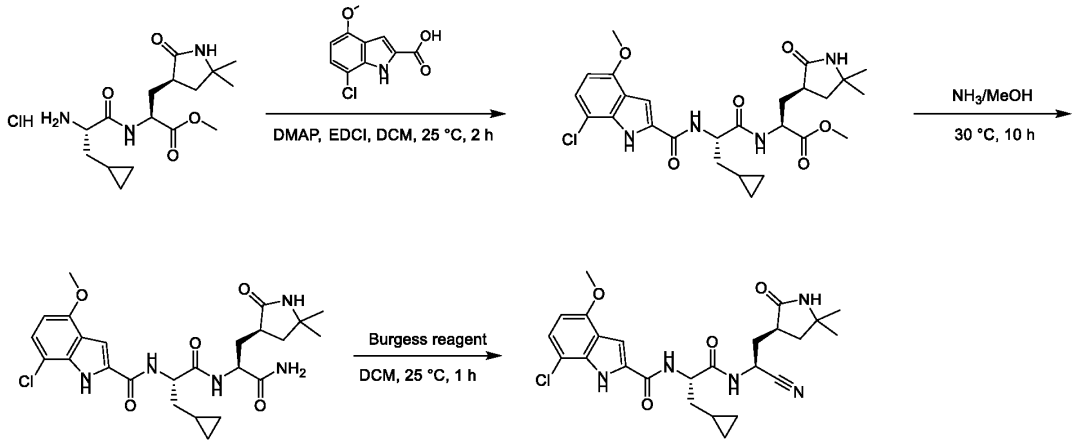
Step 3: (S)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000224] A solution of (*S*)-methyl 2-((*S*)-2-(7-chloro-4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5] decane-3-carboxamido)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (300 mg, 510.98 umol, 1 *eq*) in NH_3/MeOH (7 M, 5 mL) was stirred at 50 °C for 20 h. Upon the reaction completion, the mixture was concentrated in vacuum to obtained (*S*)-*N*-((*S*)-1-amino-3-((*R*)-5,5-dimethyl-2- oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-(7-chloro-4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (260 mg, crude) as a yellow solid. MS (ESI) *m/z* 572.3 $[M+H]^+$

[000225] Step 4: (S)-2-(7-chloro-4-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[000226] To a solution of (*S*)-*N*-((*S*)-1-amino-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-(7-chloro-4-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (260 mg, 461.46 umol, 1 *eq*) in DCM (2 mL) was added burgess reagent (329.91 mg, 1.38 mmol, 3 *eq*) and stirred at 30 °C for 1.5 h. Upon the reaction completion, the mixture was quenched by water (1 mL) and was dried by blowing N_2 and was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-65%, 10min) to obtained (*S*)-2-(7-chloro-4-methoxy-1*H*-indole-2-carbonyl)-*N*-((*S*)-1-cyano-2-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide (61.15 mg, 110.36 umol, 23.92% yield, 100% purity) as a white solid. MS (ESI) *m/z* 554.1 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.12 - 10.96 (m, 1H), 8.79 - 8.63 (m, 1H), 7.63 - 7.51 (m, 1H), 7.22 (s, 1H), 7.05 - 6.91 (m, 1H), 6.61 - 6.53 (m, 1H), 4.96 - 4.86 (m, 1H), 4.67 - 4.51 (m, 1H), 3.95 - 3.88 (m, 3H), 3.87 - 3.78 (m, 1H), 3.70 - 3.54 (m, 1H), 2.65 - 2.55 (m, 1H), 2.30 - 2.09 (m, 2H), 1.85 - 1.74 (m, 1H), 1.71 - 1.62 (m, 1H), 1.60 - 1.33 (m, 12H), 1.21 - 1.14 (m, 3H), 1.12 - 1.03 (m, 3H).

Example 273. Synthesis of viral protease inhibitor compound 1123



Step1: (S)-methyl 2-((S)-2-(7-chloro-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000227] To a solution of (*S*)-methyl 2-((*S*)-2-amino-3-cyclopropylpropanamido)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate hydrochloride (130 mg, 359.25 umol, 1.1 *eq*, HCl) in DCM (5 mL) was added 7-chloro-4-methoxy-1H-indole-2-carboxylic

acid (73.69 mg, 326.59 umol, 1 *eq*), DMAP (119.70 mg, 979.78 umol, 3 *eq*) and EDCI (125.22 mg, 653.19 umol, 2 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was quenched by H_2O (20 mL), and was extracted with DCM (10 mL * 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered, concentrated in vacuum and purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give product (*S*)-methyl 2-((*S*)-2-(7-chloro-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (150 mg, 281.42 umol, 86.17% yield) as yellow solid. MS (ESI) *m/z* 533.2 $[M+H]^+$

Step2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-4-methoxy-1H-indole-2-carboxamide

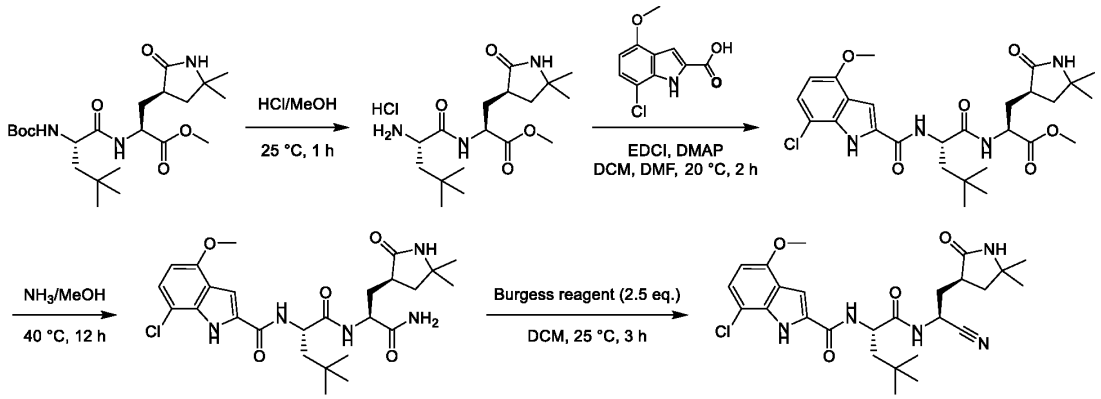
[000228] A solution of (*S*)-methyl 2-((*S*)-2-(7-chloro-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (150 mg, 281.42 umol, 1 *eq*) in ammonia (in MeOH solution, 7 M, 20 mL, 497.48 *eq*) was stirred at 30 °C for 10 h. Upon completion, the reaction was concentrated in the vacuum to give product N-((*S*)-1-(((*S*)-1-amino-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-4-methoxy-1H-indole-2-carboxamide (130 mg, crude) as yellow solid. MS (ESI) *m/z* 518.2 $[M+H]^+$

Step3: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000229] To a solution of N-((*S*)-1-(((*S*)-1-amino-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-4-methoxy-1H-indole-2-carboxamide (130 mg, 250.96 umol, 1 *eq*) in DCM (10 mL) was added burgess reagent (179.42 mg, 752.89 umol, 3 *eq*) and the mixture was stirred at 25 °C for 1 h. Upon completion, the mixture was concentrated in the vacuum and purified by prep-HPLC (column: Phenomenex Gemini-NX 80* 40 mm* 3 um; mobile phase: [water (10 mM NH_4HCO_3)- ACN]; B%: 20%-50%, 8 min) to give product 7-chloro-N-((*S*)-1-(((*S*)-1-cyano-2-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-1H-indole-2-carboxamide (40 mg, 80.00 umol, 31.88% yield, 100% purity) as white solid. MS (ESI) *m/z* 500.1 $[M+H]^+$ ^1H

NMR (400 MHz, DMSO-d_6) δ = 8.99 - 8.97 (m, 1H), 8.67 - 8.65 (m, 1H), 7.82 (s, 1H), 7.29 - 7.16 (m, 2H), 6.57 - 6.55(m, 1H), 4.99 - 4.93 (m, 1H), 4.56 - 4.37 (m, 1H), 3.89 (s, 3H), 2.61 (br s, 1H), 2.23 - 2.12 (m, 1H), 2.01 - 1.97 (m, 1H), 1.87 - 1.72 (m, 2H), 1.55 - 1.43 (m, 2H), 1.15 (s, 3H), 1.07 (s, 3H), 0.83 - 0.81 (m, 1H), 0.44 - 0.42 (m, 2H), 0.25 - 0.05 (m, 2H)

Example 274. Synthesis of viral protease inhibitor compound 1131



Step 1: (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000230] A solution of methyl (2S)-2-[[(2S)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (260 mg, 588.82 umol, 1 eq) in HCl/MeOH (4 M, 5 mL, 33.97 eq) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the procduct methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (210 mg, crude, HCl) as a white solid.

Step 2: (S)-methyl 2-((S)-2-(7-chloro-4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000231] To a solution of methyl (2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (210 mg, 555.69 umol, 1 eq, HCl) and 7-chloro-4-methoxy-1H-indole-2-carboxylic acid (162.99 mg, 722.40 umol, 1.3 eq) in DCM (5 mL) and DMF (1.5 mL), was added with DMAP (203.67 mg, 1.67 mmol, 3 eq) and EDCI (213.05 mg, 1.11 mmol, 2 eq), and then the resulting mixture

was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM 150 mL (50 mL * 3). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give the product methyl (2S)-2-[[(2S)-2-[(7-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (270 mg, 393.40 umol, 70.79% yield, 80% purity) as a yellow solid. MS (ESI) *m/z* 549.2 $[M+H]^+$.

Step 3: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-4-methoxy-1H-indole-2-carboxamide

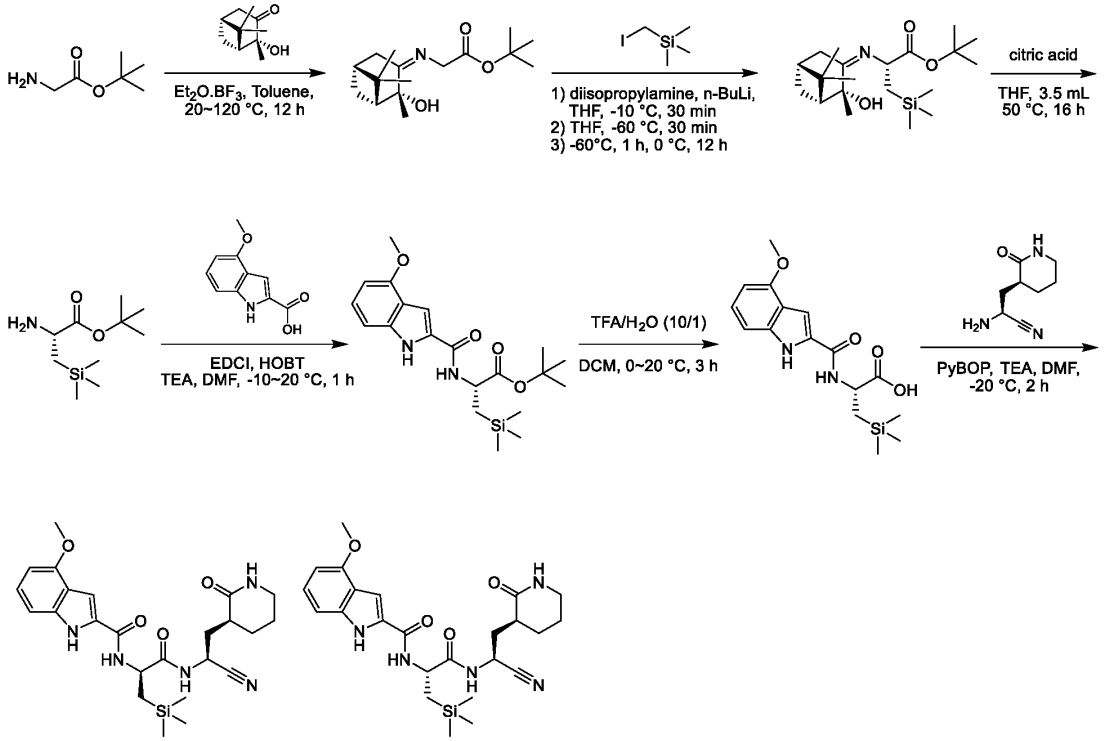
[000232] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (270.00 mg, 491.75 umol, 1 eq) in NH_3/MeOH (7 M, 5 mL, 71.17 eq), was stirred at 40 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product N-[(1S)-1-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-chloro-4-methoxy-1H-indole-2-carboxamide (240 mg, crude) as a yellow solid. MS (ESI) *m/z* 534.2 $[M+H]^+$.

Step 4: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000233] To a solution of N-[(1S)-1-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-3,3-dimethyl-butyl]-7-chloro-4-methoxy-1H-indole-2-carboxamide (240 mg, 373.00 umol, 83% purity, 1 eq) in DCM (5 mL) was added burgess reagent (222.22 mg, 932.50 umol, 2.5 eq), and then the mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xtimate C18 10u 250 mm * 80 mm; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 25%-55%, 35 min) to give the product 7-chloro-N-[(1S)-1-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1H-indole-2-carboxamide (107.95 mg, 207.10 umol, 55.52% yield, 99% purity) as a white solid. MS (ESI) *m/z* 516.2 $[M+H]^+$. ^1H NMR

(400 MHz, DMSO-d_6) δ =11.67 (br s, 1H), 8.99 (d, J = 7.9 Hz, 1H), 8.64 (d, J = 7.9 Hz, 1H), 7.82 (s, 1H), 7.27 (s, 1H), 7.20 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 4.94 (br d, J = 7.5 Hz, 1H), 4.54 (br d, J = 6.8 Hz, 1H), 3.88 (s, 3H), 2.58 - 2.53 (m, 1H), 2.21 - 2.14 (m, 1H), 1.94 (dd, J = 8.4, 12.2 Hz, 1H), 1.77 (td, J = 3.3, 6.4 Hz, 1H), 1.72 (br d, J = 6.4 Hz, 2H), 1.49 (t, J = 11.4 Hz, 1H), 1.13 (s, 3H), 1.01 (s, 3H), 0.94 (s, 9H)

Example 275. Synthesis of viral protease inhibitor compound 1133



Step 1: 2-[(Z)-[(2R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-ylidene]amino]acetate

[000234] To a solution of tert-butyl 2-aminoacetate (5.75 g, 43.84 mmol, 1.47 eq) and (2R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-one (5 g, 29.72 mmol, 1 eq) in toluene (135 mL) was added $BF_3.Et_2O$ (513.39 mg, 3.62 mmol, 446.43 uL, 1.22e^{-1} eq) at 20 °C. Then the reaction was stirred at 120 °C for 12 h in the presence with a Dean-Stark trap. Upon completion, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 5/1, 1% TEA) to give tert-butyl 2-[(Z)-[(2R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-ylidene]amino]acetate (6 g, 21.32 mmol, 71.74% yield) as a yellow oil.

Step 2: tert-butyl (2R)-2-[(Z)-[(2R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-ylidene]amino]-3-trimethylsilyl-propanoate

[000235] To a solution of N-isopropylpropan-2-amine (4.67 g, 46.20 mmol, 6.53 mL, 2.5 eq) in dry THF (100 mL) was added very slowly a solution of n-BuLi (2.5 M, 18.48 mL, 2.5 eq) at -10 °C. After 30 min, the mixture was cooled to -60 °C and the tert-butyl 2-[(Z)-[(2R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-ylidene]amino]acetate (5.2 g, 18.48 mmol, 1 eq) dissolved in THF (10 mL) was added. After 30 min, the iodomethyl(trimethyl)silane (7.12 g, 33.26 mmol, 4.95 mL, 1.8 eq) was added. The mixture was stirred at -60 °C for 1 h. Then the mixture was allowed to coolled to 0 °C for 12 h. Upon completion, the reaction was quenched with a saturated solution of ammonium chloride (40 mL). Then the aqueous phase was extracted with ethyl acetate (20 mL * 3). The organic phase was dried over Na_2SO_4, filtered and concnetrated in vacuo to dryness. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 10/1, 1% TEA) to give tert-butyl (2R)-2-[(Z)-[(2R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-ylidene]amino]-3-trimethylsilyl-propanoate (3.4 g, 8.32 mmol, 45.05% yield, 90% purity) as a yellow oil.

Step 3: tert-butyl (2R)-2-amino-3-trimethylsilyl-propanoate

[000236] To a solution of the tert-butyl (2R)-2-[(Z)-[(2R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-ylidene]amino]-3-trimethylsilyl-propanoate (0.65 g, 1.77 mmol, 1 eq) in THF (3.5 mL) was added a solution of Citric acid (10 mL, 15% purity). The mixture was stirred at 50 °C for 16 h. Upon completion, after removing THF in vacuo, the aqueous layer was extracted with EtOAc (15 mL) in order to remove the chiral inductor. Then the pH was increased to 8-9 with potassium carbonate addition. The free amine was then extracted with EtOAc (30 mL * 3). The organic layer was combained, dried over Na_2SO_4, concentrated at room temperature due to the amine volatility to give tert-butyl (2R)-2-amino-3-trimethylsilyl-propanoate (380 mg, crude) as a yellow oil

Step 4: tert-butyl (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoate

[000237] To a solution of 4-methoxy-1H-indole-2-carboxylic acid (380 mg, 1.99 mmol, 1 eq) in DMF (5 mL) was added tert-butyl (2R)-2-amino-3-trimethylsilyl-propanoate (380 mg, 1.75 mmol, 8.79e-1 eq), EDCI (495.34 mg, 2.58 mmol, 1.3 eq), TEA (603.38 mg, 5.96 mmol, 829.96 uL, 3 eq). Then the reaction was added HOBt (349.14 mg, 2.58 mmol, 1.3 eq) at -10~0 °C for 10 min. Then the reaction was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (100 mL) and extracted with EA 150 mL (50 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was pruified by column (SiO_2, PE/EA = 10/1 to 1/1) to give tert-butyl (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoate (600 mg, 1.54 mmol, 77.29% yield, assumed 100% purity) as a white solid.

Step 5: (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoic acid

[000238] To a solution of tert-butyl (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoate (300 mg, 768.15 umol, 1 eq) in DCM (3 mL) was added TFA/H_2O (2 mL, 10/1) at 0 °C. Then the reaction was stirred at 20 °C for 3 h. Upon completion, the reaction was concentrated in vacuo to dryness below 30 °C to dryness. The reaction mixture was quenched by addition EA (30 mL) at 20 °C, and then diluted with H_2O (20 mL) and extracted with EA 20 mL (10 mL * 2). The combined organic layers were washed with sat. NaCl 20 mL (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue of (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoic acid (300 mg, crude) as a yellow oil.

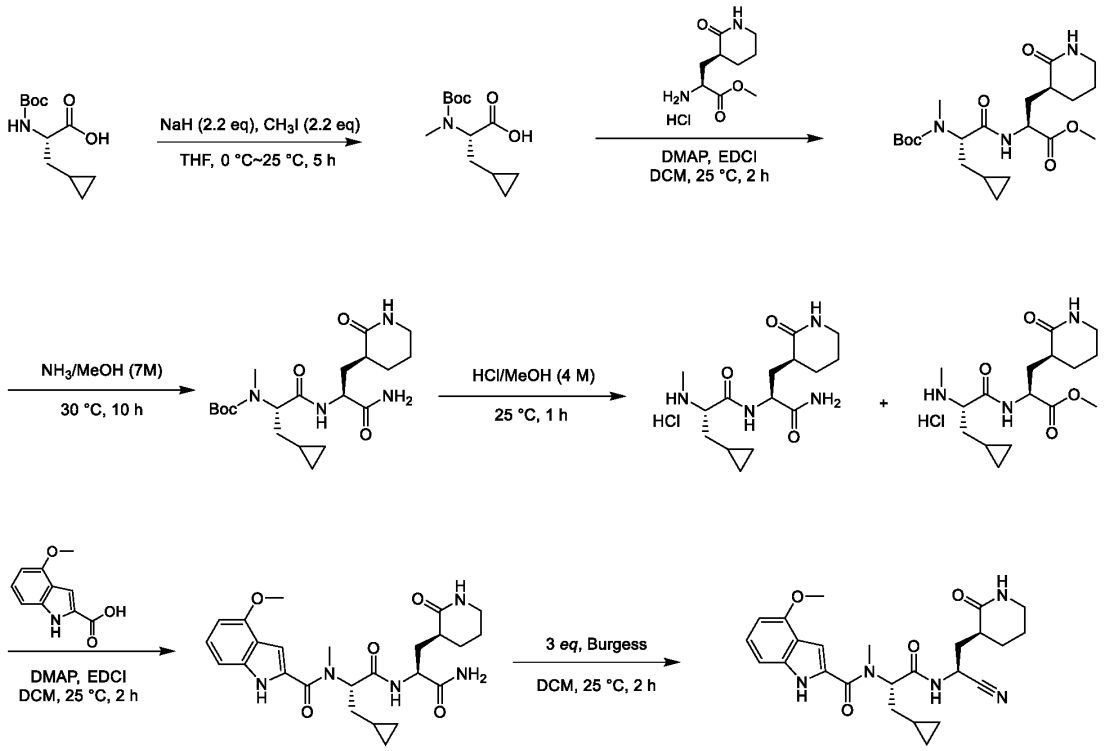
Step 6: N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-2-oxo-1-(trimethylsilylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide Isomer 1 & N-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-2-oxo-1-(trimethylsilylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide Isomer 2

[000239] To a solution of (2R)-2-[(4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoic acid (230 mg, 687.71 umol, 1 eq) and (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanenitrile (114.99 mg, 687.71 umol, 1 eq) in DMF (3 mL) was added PyBop (357.88 mg, 687.71 umol, 1 eq) and TEA (139.18 mg, 1.38 mmol, 191.44 uL, 2 eq) in DMF (1 mL) at -20 °C. Then the reaction was stirred at -20 °C for

2 h. Upon completion, the reaction was diluted with MeCN (2 mL), filtered. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 40%-70%,8min) to give ~70 mg epimerisomers. Then the residue was seperated by SFC (column: DAICEL CHIRALCEL OD(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O MEOH];B%: 30%-30%,15min) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-2-oxo-1-(trimethylsilylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide Isomer 1 (20 mg, 40.53 umol, 5.89% yield, 98% purity) as a white solid. MS (ESI) *m/z* 484.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.23 (s, 1H), 7.19 - 7.10 (m, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.04 (dd, *J* = 6.3, 9.9 Hz, 1H), 4.60 (t, *J* = 8.0 Hz, 1H), 3.94 (s, 3H), 3.21 - 3.11 (m, 2H), 2.45 - 2.23 (m, 2H), 2.05 - 1.95 (m, 1H), 1.90 (td, *J* = 6.8, 13.6 Hz, 1H), 1.82 (dt, *J* = 3.9, 9.0 Hz, 1H), 1.73 - 1.60 (m, 1H), 1.57 - 1.43 (m, 1H), 1.25 - 1.15 (m, 2H), 0.10 (s, 9H).

[000240] To give N-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-2-oxo-1-(trimethylsilylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide Isomer 2 (70 mg, 144.74 umol, 21.05% yield, 100% purity) as a white solid. MS (ESI) *m/z* 484.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.23 (s, 1H), 7.19 - 7.10 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 5.09 (dd, *J* = 6.1, 9.8 Hz, 1H), 4.61 (t, *J* = 7.9 Hz, 1H), 3.93 (s, 3H), 3.22 - 3.17 (m, 2H), 2.52 - 2.37 (m, 2H), 2.02 - 1.88 (m, 2H), 1.83 - 1.74 (m, 1H), 1.72 - 1.60 (m, 1H), 1.57 - 1.42 (m, 1H), 1.21 (d, *J* = 8.0 Hz, 2H), 0.16 - 0.05 (m, 9H).

Example 276. Synthesis of viral protease inhibitor compound 1135



Step1: (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanoic acid

[000241] A solution of (2*S*)-2-(tert-butoxycarbonylamino)-3-cyclopropyl-propanoic acid (6 g, 26.17 mmol, 1 *eq*) in THF (60 mL) was cooled at 0 °C and was added NaH (2.30 g, 57.57 mmol, 60% purity, 2.2 *eq*) and the mixture was warmed at 25 °C and stirred for 1.5 h, then was added CH_3I (8.17 g, 57.57 mmol, 3.58 mL, 2.2 *eq*) and stirred for 2.5 h. Upon completion, the mixture was quenched by H_2O (200 mL) and was adjusted pH = 1 with HCl (1 M), and extracted with ethyl acetate (150 mL * 3). The combined organic phase was washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude product (*S*)-2-((tert-butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanoic acid (6.17 g, crude) as yellow oil. MS (ESI) *m/z* 244.1 $[M+H]^+$

Step2: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000242] To a solution of (*S*)-2-((tert-butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanoic acid (6.17 g, 25.36 mmol, 1 *eq*) in DCM (100 mL) was added (*S*)-methyl 2-amino-3-((*S*)-2-oxopiperidin-3-yl)propanoate (6.60 g, 27.90 mmol, 1.1

eq, HCl), was added DMAP (9.29 g, 76.08 mmol, 3 *eq*) and EDCI (9.72 g, 50.72 mmol, 2 *eq*), and then the mixture was stirred at 25 °C for 2 h. Upon completion, the mixture was quenched by H_2O (200 mL) and was extracted with DCM (200 mL * 3). The combined organic phase was washed with brine (200 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/10 to 0/1) to give product (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (7 g, 16.45 mmol, 64.87% yield) as yellow oil. MS (ESI) *m/z* 426.3 $[M+H]^+$

Step3: tert-butyl ((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)(methyl)carbamate

[000243] To a solution of (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1.02 g, 2.40 mmol, 1 *eq*) in AMMONIA (7 M, 40 mL, 116.81 *eq*) was stirred at 30 °C for 10 h. Upon completion, the reaction was concentrated in the vacuum to give crude product tert-butyl ((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)(methyl)carbamate (990 mg, crude) as yellow solid. MS (ESI) *m/z* 411.3 $[M+H]^+$

Step4: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-cyclopropyl-2-(methylamino)propanamide; (S)-methyl 2-((S)-3-cyclopropyl-2-(methylamino)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000244] To a solution of tert-butyl ((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)(methyl)carbamate (990 mg, 2.41 mmol, 1 *eq*) in HCl/MeOH (30 mL) was stirred at 25 °C for 1 h. Upon completion. the reaction was concentrated in the vacuum to give crude product (*S*)-N-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)-3-cyclopropyl-2-(methylamino)propanamide (1.1 g, crude, 30% purity) as yellow solid (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(methylamino)propanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1.1 g, crude, 60% purity) as yellow solid. MS (ESI) *m/z* 311.2 $[M+H]^+$, MS (ESI) *m/z* 326.2 $[M+H]^+$

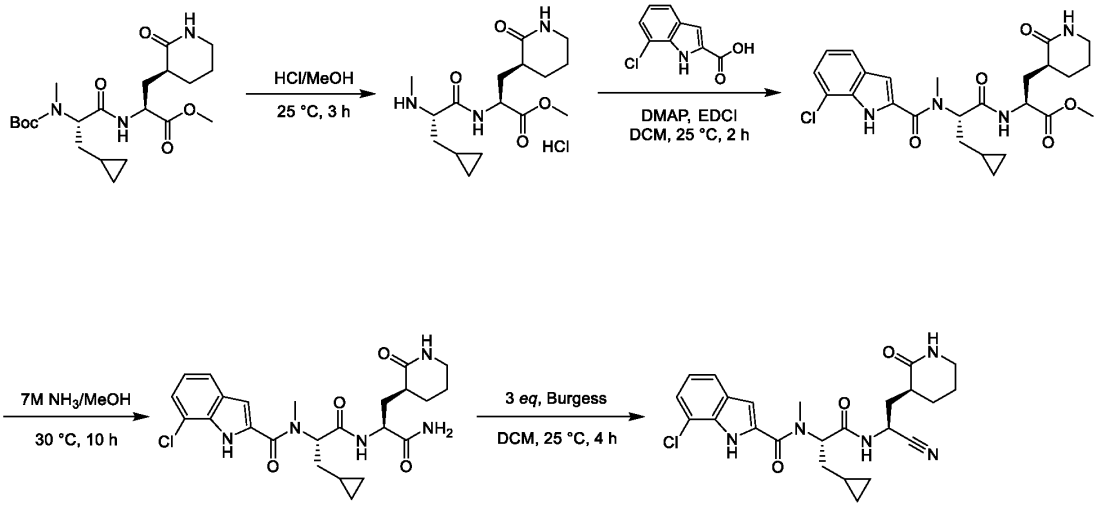
Step5: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-N-methyl-1H-indole-2-carboxamide

[000245] To a solution of (*S*)-N-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)-3-cyclopropyl-2-(methylamino)propanamide (1 g, 966.52 umol, 30% purity, 1 *eq*), 4-methoxy-1H-indole-2-carboxylic acid (184.78 mg, 966.52 umol, 1 *eq*) in DCM (30 mL) was added DMAP (354.24 mg, 2.90 mmol, 3 *eq*), EDCI (370.56 mg, 1.93 mmol, 2 *eq*) and the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was quenched by H_2O (200 mL), and was extracted with DCM (100 mL * 3). The combined organic phase was washed with brine (200 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give product N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-N-methyl-1H-indole-2-carboxamide (90 mg, 186.12 umol, 19.26% yield) as yellow solid. MS (ESI) *m/z* 484.2 $[M+H]^+$

Step6: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-N-methyl-1H-indole-2-carboxamide

[000246] To a solution of N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-N-methyl-1H-indole-2-carboxamide (86 mg, 177.85 umol, 1 *eq*) in DCM (3 mL) was added burgess reagent (127.15 mg, 533.54 umol, 3 *eq*) and the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was concentrated in the vacuum and was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 20%-50%,8min) to give product N-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-methoxy-N-methyl-1H-indole-2-carboxamide (35 mg, 75.18 umol, 42.27% yield, 100% purity) as white solid. MS (ESI) *m/z* 466.1 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ = 11.60 (br s, 1H), 8.87 (br s, 1H), 7.56 (br s, 1H), 7.15 - 7.07 (m, 1H), 7.05 - 6.99 (m, 1H), 6.91 (br s, 1H), 6.52 - 6.50 (m, 1H), 5.13 - 4.96 (m, 2H), 3.87 (s, 3H), 3.09 (br s, 2H), 2.23 (br s, 2H), 1.96 - 1.77 (m, 3H), 1.74 - 1.71 (m, 1H), 1.66 - 1.34 (m, 3H), 0.80 - 0.02 (m, 5H)

Example 277. Synthesis of viral protease inhibitor compound 1137



Step1: (S)-methyl 2-((S)-3-cyclopropyl-2-(methylamino)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000247] To a solution of (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (2 g, 4.70 mmol, 1 *eq*) in HCl/MeOH (50 mL) was stirred at 25 °C for 3 h. Upon completion, the reaction was concentrated in the vacuum to give crude product (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(methylamino)propanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (2 g, crude) as yellow solid. MS (ESI) *m/z* 326.2 $[M+H]^+$

Step2: (S)-methyl 2-((S)-2-(7-chloro-N-methyl-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000248] To a solution of (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(methylamino)propanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (1 g, 2.76 mmol, 1 *eq*, HCl) in DCM (30 mL) was added 7-chloro-1H-indole-2-carboxylic acid (540.54 mg, 2.76 mmol, 1 *eq*), DMAP (1.01 g, 8.29 mmol, 3 *eq*), EDCI (1.06 g, 5.53 mmol, 2 *eq*) and the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was quenched by H_2O (200 mL), and was extracted with DCM (100 mL * 3). The combined organic phase was washed with brine (200 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/9 to 0/1) to give product (*S*)-methyl 2-((*S*)-2-(7-chloro-N-methyl-1H-indole-2-carboxamido)-3-

cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (530 mg, 1.05 mmol, 38.13% yield) as yellow solid. MS (ESI) *m/z* 503.2 $[M+H]^+$

Step3: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-N-methyl-1H-indole-2-carboxamide

[000249] A solution of (*S*)-methyl 2-((*S*)-2-(7-chloro-N-methyl-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (530 mg, 1.05 mmol, 1 *eq*) in ammonia (7 M, 30 mL, 199.30 *eq*) was stirred at 30 °C for 10 h. Upon completion, the reaction was concentrated in the vacuum to give crude prodcut N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-N-methyl-1H-indole-2-carboxamide (440 mg, crude) as yellow solid. MS (ESI) *m/z* 488.2 $[M+H]^+$

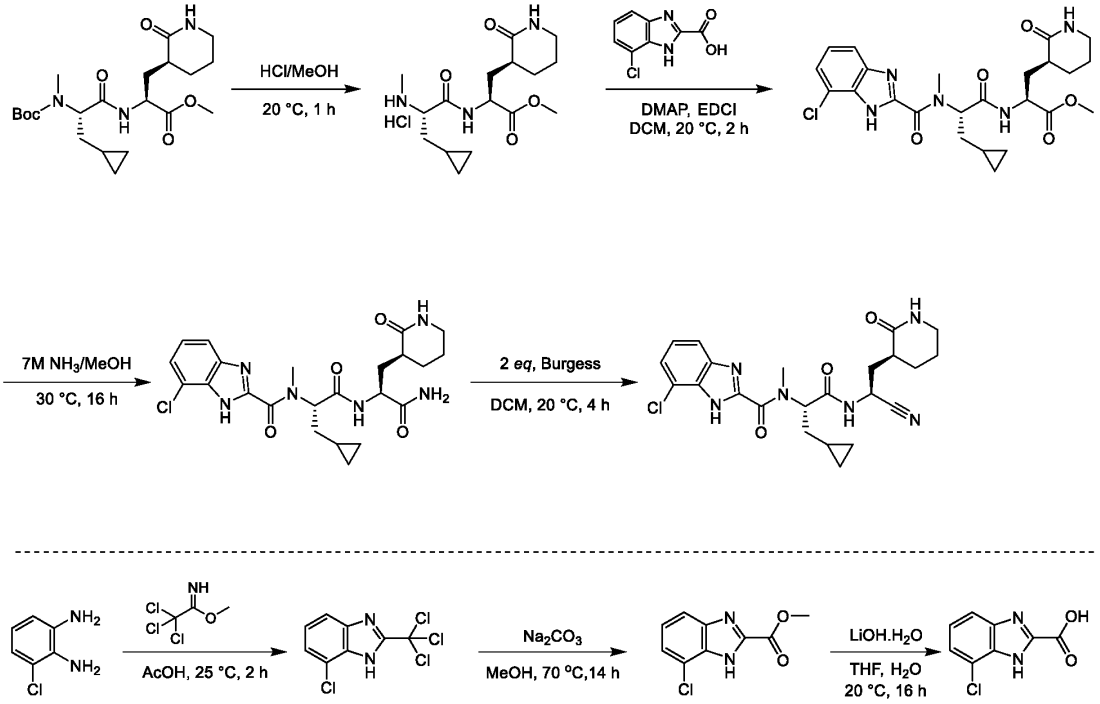
Step4: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-(trifluoromethyl)-1H-indole-2-carboxamide

[000250] To a solution of N-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-N-methyl-1H-indole-2-carboxamide (440 mg, 901.68 umol, 1 *eq*) in DCM (15 mL) was added burgess reagent (644.62 mg, 2.71 mmol, 3 *eq*) and the mixture was stirred at 25 °C for 4 h. Upon completion, the reaction was concentrated in the vacuum and was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 30%-60%,8min) to give product 7-chloro-N-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-N-methyl-1H-indole-2-carboxamide (220 mg, 468.12 umol, 51.92% yield, 100% purity) as white solid. MS (ESI) *m/z* 470.1 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ = 11.93 - 11.60 (m, 1H), 8.90 (br s, 1H), 7.57 (br s, 2H), 7.28 - 7.26 (m, 1H), 7.08 - 7.04 (m, 1H), 7.02 - 6.57 (m, 1H), 5.12 - 5.02 (m, 1H), 5.00 - 4.71 (m, 1H), 3.30 - 3.16 (m, 2H), 3.13 - 2.93 (m, 3H), 2.30 - 2.16 (m, 2H), 1.95 - 1.39 (m, 7H), 0.84 - 0.18 (m, 5H).

[000251] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.34 (br s, 1H), 8.73 - 8.71 (m, 1H), 7.61 - 7.59 (m, 1H), 7.35 - 7.23 (m, 2H), 7.10 - 7.02 (m, 1H), 6.87 (br s, 1H), 5.07 - 5.01 (m, 1H), 4.93 (br s, 1H), 3.14 (br s, 5H), 2.34 - 2.19 (m, 2H), 1.98 - 1.81 (m, 3H), 1.80 -

1.56 (m, 3H), 1.51 - 1.44 (m, 1H), 0.71 (br s, 1H), 0.53 - 0.37 (m, 1H), 0.53 - 0.37 (m, 1H), 0.19 - 0.04 (m, 2H)

Example 278. Synthesis of viral protease inhibitor compound 1141



Step 1: 7-chloro-2-(trichloromethyl)-1H-benzo[d]imidazole

[000252] To a solution of 3-chlorobenzene-1,2-diamine (2 g, 14.03 mmol, 1 eq) in AcOH (20 mL) was added methyl 2,2,2-trichloroethanimidate (2.97 g, 16.83 mmol, 2.08 mL, 1.2 eq). The mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched by addition of sat. $NaHCO_3$ (50 mL) to adjust the pH=7-8, and then extracted with ethyl acetate (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the product 7-chloro-2-(trichloromethyl)-1*H*-benzimidazole (3 g, crude) as a yellow solid. MS (ESI) *m/z* 270.9 $[M+H]^+$

Step 2: methyl 7-chloro-1H-benzo[d]imidazole-2-carboxylate

[000253] To a solution of 7-chloro-2-(trichloromethyl)-1*H*-benzimidazole (3 g, 11.11 mmol, 1 eq) in MeOH (40 mL) was added Na_2CO_3 (1.18 g, 11.11 mmol, 1 eq). The mixture was stirred at 70 °C for 14 h. Upon completion, the mixture was concentrated

under the reduced pressure to give the product methyl 7-chloro-1*H*-benzimidazole-2-carboxylate (3 g, crude) as a yellow solid. MS (ESI) *m/z* 210.9 $[M+H]^+$

Step 3: 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid

[000254] To a solution of methyl 7-chloro-1*H*-benzimidazole-2-carboxylate (3 g, 14.24 mmol, 1 eq) in THF (20 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (1.79 g, 42.73 mmol, 3 eq). The mixture was stirred at 60 °C for 2 h. Upon completion, the reaction mixture was quenched by addition of 1N HCl (20 mL) to adjust the pH=3-5, and then extracted with EA (30 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the product 7-chloro-1*H*-benzimidazole-2-carboxylic acid (2 g, crude) as a yellow solid. MS (ESI) *m/z* 197.0 $[M+H]^+$

Step 4: (S)-methyl2-((S)-3-cyclopropyl-2-(methylamino)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000255] A mixture of methyl (2*S*)-2-[[(2*S*)-2-[tert-butoxycarbonyl(methyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (1 g, 2.35 mmol, 1 eq) in HCl/MeOH (4 M, 20 mL, 59.57 eq) was stirred at 20 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure to give the product methyl (2*S*)-2-[[(2*S*)-3-cyclopropyl-2-(methylamino)propanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (0.8 g, crude, HCl) as a yellow solid. MS (ESI) *m/z* 326.2 $[M+H]^+$

Step 5: (S)-methyl2-((S)-2-(7-chloro-N-methyl-1H-benzo[d]imidazole-2-carboxamido)-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000256] To a solution of methyl(2*S*)-2-[[(2*S*)-3-cyclopropyl-2-(methylamino)propanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (700 mg, 1.93 mmol, 1 eq, HCl) and 7-chloro-1*H*-benzimidazole-2-carboxylic acid (456.35 mg, 2.32 mmol, 1.2 eq) in DMF (20 mL) was added DMAP (472.65 mg, 3.87 mmol, 2 eq) and EDCI (741.67 mg, 3.87 mmol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL), and then extracted with EA (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum

ether/Ethyl acetate = 5/1 to 0/1) to give the product methyl(2*S*)-2-[[(2*S*)-2-[(7-chloro-1*H*-benzimidazole-2-carbonyl)-methyl-amino]-3-cyclopropylpropanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (0.5 g, 992.11 umol, 51.29% yield) as a yellow solid. MS (ESI) *m/z* 504.2 $[M+H]^+$

Step 6: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-chloro-N-methyl-1H-benzo[d]imidazole-2-carboxamide

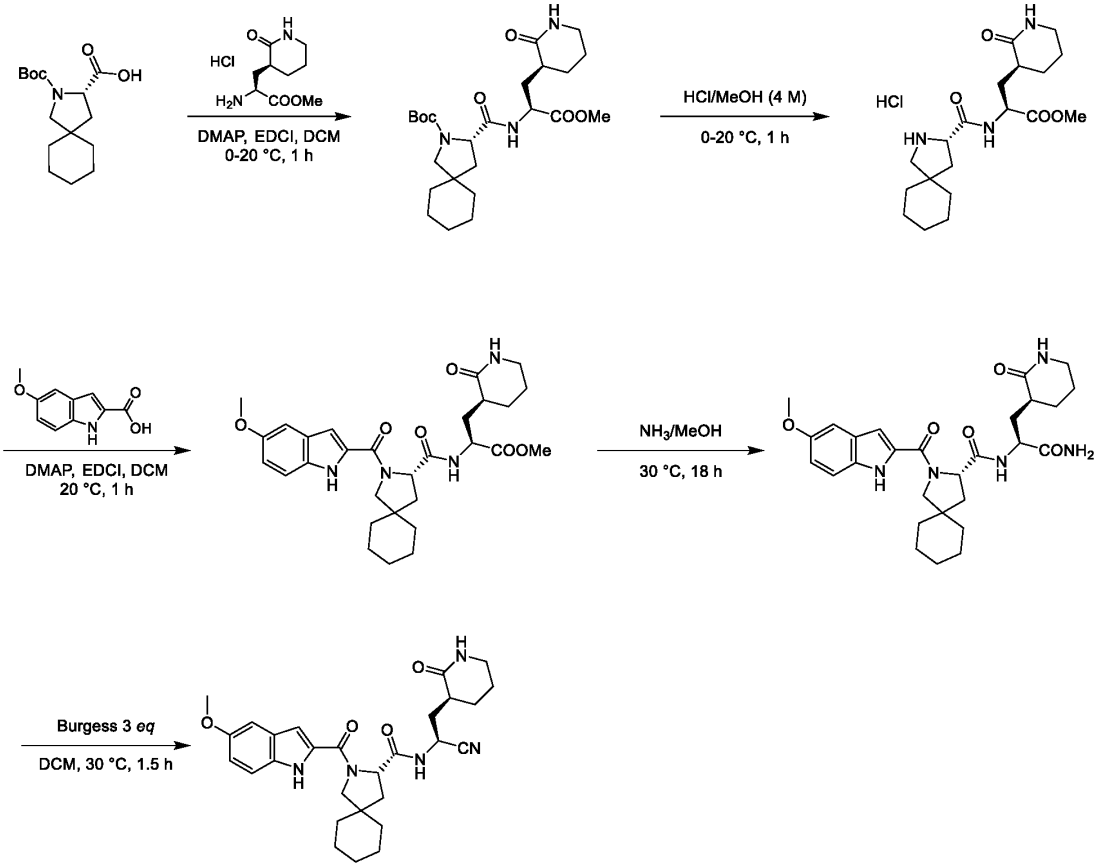
[000257] A mixture of methyl(2*S*)-2-[[(2*S*)-2-[(7-chloro-1*H*-benzimidazole-2-carbonyl)-methyl-amino]-3-cyclopropylpropanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (450 mg, 892.90 umol, 1 eq) in NH_3/MeOH (7 M, 10 mL, 78.40 eq) was stirred at 30 °C for 16 h. Upon completion, the mixture was concentrated under the reduced pressure to give the product *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-*N*-methyl-1*H*-benzimidazole-2-carboxamide (400 mg, crude) as a yellow solid. MS (ESI) *m/z* 489.2 $[M+H]^+$

Step 7: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-N-methyl-1H-benzo[d]imidazole-2-carboxamide

[000258] To a solution of *N*-[(1*S*)-2-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-*N*-methyl-1*H*-benzimidazole-2-carboxamide (200 mg, 409.03 umol, 1 eq) in DCM (10 mL) was added burgess reagent (194.95 mg, 818.05 umol, 2 eq). The mixture was stirred at 20 °C for 4 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water(10 mM NH_4HCO_3) - ACN]; B%: 30% - 60%, 8 min) to give the product 7-chloro-*N*-[(1*S*)-2-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxoethyl]-*N*-methyl-1*H*-benzimidazole-2-carboxamide (50 mg, 106.17 umol, 12.98% yield, 100% purity) as a white solid. MS (ESI) *m/z* 471.2 $[M+H]^+$ ^1H NMR (400 MHz, MeOD-d_4) δ = 7.72 - 7.48 (s, 1H), 7.45 - 7.25 (m, 3H), 5.92 (dd, *J* = 5.8, 9.2 Hz, 1H), 5.32 - 5.17 (m, 1H), 5.14 - 4.94 (m, 1H), 3.62 - 3.55 (m, 1H), 3.20 (dd, *J* = 4.6, 8.8 Hz, 3H), 3.07 (s, 3H), 2.57 - 2.33 (m, 3H), 2.12 - 1.92 (m, 4H), 1.88 - 1.77

(m, 2H), 1.74 - 1.46 (m, 4H), 0.62 - 0.39 (m, 3H), 0.35 - 0.10 (m, 3H), 0.009 - 0.037 (m, 1H).

Example 279. Synthesis of viral protease inhibitor compound 1143



Step 1: (S)-tert-butyl3-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate

[000259] To a solution of (*S*)-2-(tert-butoxycarbonyl)-2-azaspiro[4.5]decane-3-carboxylic acid (300 mg, 846.97 umol, 80% purity, 1 *eq*) in DCM (8 mL) was added (*S*)-methyl 2-amino-3-((*S*)-2-oxopiperidin-3-yl)propanoate (169.59 mg, 846.97 umol, 1 *eq*), and then DMAP (310.42 mg, 2.54 mmol, 3 *eq*) and EDCI (324.73 mg, 1.69 mmol, 2 *eq*) were added at 0 °C, then the mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the reaction mixture was quenched by addition of water (10 mL), and extracted with DCM (3 mL * 3). The combined organic layers were washed with HCl (1 M, 4 mL), then was adjusted pH~7 with sat. $NaHCO_3$ (4 mL), dried over Na_2SO_4,

filtered and concentrated in vacuum and was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to obtained (*S*)-tert-butyl3-(((*S*)-1-methoxy-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate (268 mg, 575.62 umol, 67.96% yield) as a yellow solid. MS (ESI) *m/z* 466.3 $[M+H]^+$

Step 2: (S)-methyl3-((S)-2-oxopiperidin-3-yl)-2-((S)-2-azaspiro[4.5]decane-3-carboxamido)propanoate

[000260] A solution of (*S*)-tert-butyl 3-(((*S*)-1-methoxy-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl)carbamoyl)-2-azaspiro[4.5]decane-2-carboxylate (240 mg, 515.48 umol, 1 *eq*) in HCl/MeOH (4 M, 4 mL) at 0 °C, the mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was concerntration in vacuum to obtained (*S*)-methyl3-((*S*)-2-oxopiperidin-3-yl)-2-((*S*)- 2-azaspiro[4.5]decane-3-carboxamido)propanoate (180 mg, crude, HCl) as a yellow solid. MS (ESI) *m/z* 366.2 $[M+H]^+$

Step 3: (S)-methyl2-((S)-2-(5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000261] A mixture of (*S*)-methyl 3-((*S*)-2-oxopiperidin-3-yl)-2-((*S*)-2-azaspiro[4.5]decane-3-carboxamido)propanoate (180 mg, 447.84 umol, 1 *eq*, HCl) in DCM (4 mL) was added 5-methoxy-1*H*-indole-2-carboxylic acid (85.62 mg, 447.84 umol, 1 *eq*), and then was added DMAP (109.43 mg, 895.69 umol, 2 *eq*) and EDCI (128.78 mg, 671.76 umol, 1.5 *eq*) at 20 °C, the mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the reaction mixture was quenched by addition of water (10 mL), and then extracted with DCM (3 mL * 3). The combined organic layers were washed with HCl (1 M, 4 mL), then was adjusted pH~7 with sat. $NaHCO_3$ (4 mL), dried over Na_2SO_4, filtered and concentration in vacuum and was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to obtained (*S*)-methyl2-((*S*)-2-(5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (220 mg, 408.44 umol, 91.20% yield) as a yellow solid. MS (ESI) *m/z* 539.3 $[M+H]^+$

Step 4: (S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

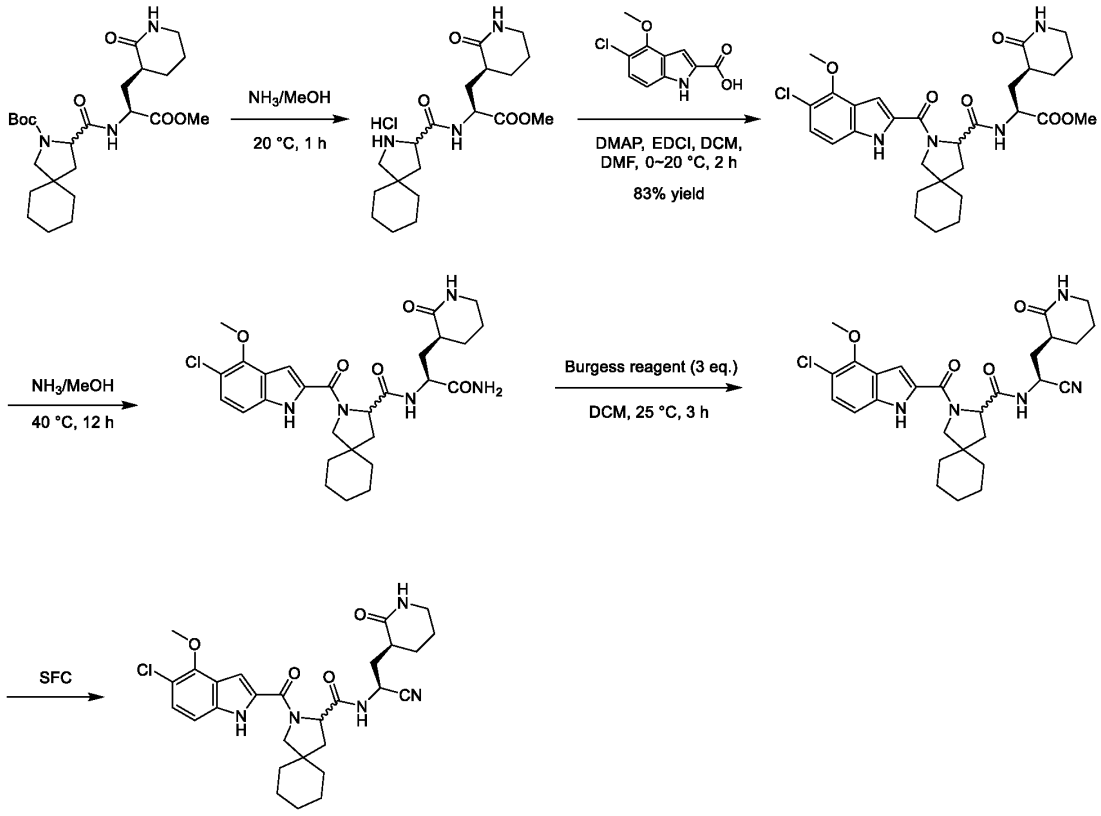
[000262] A solution of (*S*)-methyl 2-((*S*)-2-(5-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro [4.5] decane-3-carboxamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (200 mg, 371.31 umol, 1 *eq*) was added with NH_3/MeOH (7 M, 5 mL), and then the mixture was stirred at 30 °C for 18 h. Upon the reaction completion, the reaction mixture was concentration in vacuum to obtained (*S*)-*N*-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)-2-(5-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (150 mg, crude) as a yellow solid. MS (ESI) *m/z* 524.3 $[M+H]^+$

Step 5: (S)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-(5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000263] To a solution of (*S*)-*N*-((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl) propan-2-yl)-2-(5-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (150 mg, 286.47 umol, 1 *eq*) in DCM (3 mL) was added burgess reagent (204.80 mg, 859.40 umol, 3 *eq*) and stirred at 30 °C for 1.5 h. Upon the reaction completion, the reaction mixture was quenced by water (1 mL) and was dried by blowing N_2 and was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 30%-60%, 10min) to obtained (*S*)-*N*-((*S*)-1-cyano-2-((*S*)-2-oxopiperidin-3-yl)ethyl)-2-(5-methoxy-1*H*-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (10.54 mg, 20.85 umol, 7.28% yield, 100% purity) as a white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.44 - 11.33 (m, 1H), 9.11 - 8.84 (m, 1H), 7.58 - 7.41 (m, 1H), 7.36 - 7.24 (m, 1H), 7.15 (d, *J* = 1.5 Hz, 1H), 6.98 - 6.92 (m, 1H), 6.89 - 6.76 (m, 1H), 4.89 (s, 1H), 4.54 - 4.45 (m, 1H), 3.94 - 3.84 (m, 1H), 3.75 (s, 3H), 3.72 (s, 1H), 2.88 (s, 2H), 2.30 - 2.23 (m, 1H), 2.22 - 2.14 (m, 1H), 2.03 - 1.82 (m, 1H), 1.81 - 1.63 (m, 2H), 1.59 - 1.12 (m, 14H).

[000264] ^1H NMR (400 MHz, DMSO-d_6, 273+80K) δ ppm 11.14 (s, 1H), 8.72 (s, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.27 (s, 1H), 7.09 (s, 1H), 6.86 (dd, *J* = 1.9, 8.9 Hz, 2H), 5.03 - 4.91 (m, 1H), 4.69 - 4.54 (m, 1H), 3.89 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 3.66 - 3.51 (m, 1H), 2.30 - 2.10 (m, 3H), 1.86 - 1.62 (m, 4H), 1.59 - 1.36 (m, 14H).

Example 280. Synthesis of viral protease inhibitor compound 1145



Step 1: (2S)-methyl 3-((S)-2-oxopiperidin-3-yl)-2-(2-azaspiro[4.5]decane-3-carboxamido)propanoate hydrochloride

[000265] A solution of tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carboxylate (3.5 g, 7.52 mmol, 1 eq) in HCl/MeOH (4 M, 50 mL, 26.60 eq) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (3 g, crude, HCl) was obtained as a white solid.

Step 2: (2S)-methyl 2-(2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000266] To a solution of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.59 g, 3.96 mmol, 9.92 e-1 eq, HCl) and 5-chloro-4-methoxy-1H-indole-2-carboxylic acid (900 mg, 3.99 mmol, 1 eq) in DCM (15 mL) and DMF (5 mL) was added DMAP (1.46 g, 11.97 mmol, 3 eq) and EDCI (1.53 g, 7.98 mmol, 2 eq) at 0 °C, and then the resulting mixture was stirred at 20 °C

for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM 150 mL (50 mL * 3). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 5:1 to 0:1) to give the product methyl (2S)-2-[[2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (2 g, 3.35 mmol, 83.99% yield, 96% purity) as a yellow solid. MS (ESI) *m/z* 573.2 $[M+H]^+$.

Step 3: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000267] A solution of methyl (2S)-2-[[2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.95 g, 3.40 mmol, 1 eq) in NH_3/MeOH (7 M, 50 mL, 102.86 eq) stirred at 40 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.8 g, crude) as a white solid. MS (ESI) *m/z* 558.2 $[M+H]^+$.

Step 4: 2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

[000268] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.80 g, 3.23 mmol, 1 eq) in DCM (25 mL) was added burgess reagent (2.31 g, 9.68 mmol, 3 eq), and then the resulting mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xtimate C18 10u 250 mm * 80mm;mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 25%-55%, 35 min) to give the product 2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (1.5 g, 2.75 mmol, 85.25% yield, 99% purity) as a white solid. MS (ESI) *m/z* 540.2 $[M+H]^+$.

Step 5: 2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-2-azaspiro[4.5]decane-3-carboxamide

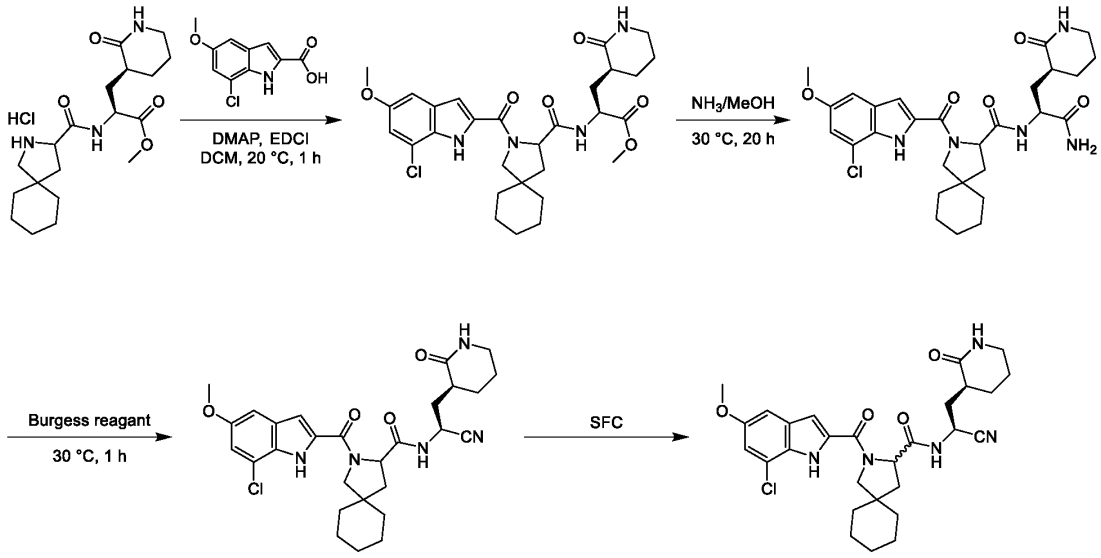
[000269] 2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (1.5 g) was separated by SFC (column: REGIS(S,S)WHELK-O1(250 mm * 25 mm,10 um); mobile phase: [0.1% NH_3H_2O MEOH]; B%: 50%-50%, 4 min) to give the product 2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (308.55 mg, 569.62 umol, 20.51% yield, 99.7% purity) as a white solid. MS (ESI) *m/z* 540.2 $[M+H]^+$.

[000270] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.23 - 6.86 (m, 3H), 5.09 - 5.00 (m, 1H), 4.63 (dd, *J* = 8.0, 9.5 Hz, 1H), 4.10 - 4.02 (m, 3H), 3.94 (br s, 1H), 3.80 (d, *J* = 10.3 Hz, 1H), 3.23 - 3.01 (m, 2H), 2.42 - 2.05 (m, 3H), 2.01 - 1.38 (m, 16H)

[000271] To give the product 2-(5-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide Isomer 2 (269.63 mg, 499.27 umol, 17.98% yield, 100% purity) as a white solid. MS (ESI) *m/z* 540.2 $[M+H]^+$.

[000272] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.25 - 6.82 (m, 3H), 5.11 (dd, *J* = 5.7, 10.5 Hz, 1H), 4.62 (dd, *J* = 7.9, 9.6 Hz, 1H), 4.01 (s, 3H), 4.00 - 3.82 (m, 1H), 3.75 (d, *J* = 10.1 Hz, 1H), 3.28 - 3.05 (m, 2H), 2.62 - 1.69 (m, 7H), 1.68 - 1.33 (m, 12H)

Example 281. Synthesis of viral protease inhibitor compound 1147



Step 1: methyl (2S)-2-[[2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000273] A mixture of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.4 g, 3.48 mmol, 1 *eq*, HCl) in DCM (20 mL) then added 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (1.2 g, 5.32 mmol, 1.53 *eq*), DMAP (1.06 g, 8.71 mmol, 2.5 *eq*) and EDCI (1.34 g, 6.97 mmol, 2 *eq*) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, PE:EA = 2:1 to 0:1) to get product methyl (2S)-2-[[2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.3 g, 2.27 mmol, 65.13% yield) as yellow solid. MS (ESI) m/z 573.2 $[M+H]^+$.

[000274] Step 2: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000275] A mixture of methyl (2S)-2-[[2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (1.26 g, 2.20 mmol, 1 *eq*) in NH_3/MeOH (7 M, 20 mL, 63.68 *eq*) was stirred at 30 °C for 20 h. Upon completion, the mixture was concentrated under reduced pressure to give a

residue, then was dissolved with DCM (30 mL * 3) and concentrated under reduced pressure to get the product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.2 g, crude) as yellow solid. MS (ESI) m/z 558.3 $[M+H]^+$.

[000276] Step 3: 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[000277] A mixture of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (1.20 g, 2.15 mmol, 1 *eq*) in DCM (20 mL) added BURGESS REAGENT (1.49 g, 6.24 mmol, 2.9 *eq*) was stirred at 30 °C for 1 h. Upon completion, the mixture were quenched with water (1 mL) and blow-dried with N_2. The residue was purified by prep-HPLC (column: Waters X bridge C18 150 * 50 mm * 10um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 35% - 65%, 10 min), which was further separated by SFC (column: REGIS (S,S)WHELK-O1 (250 mm * 25 mm, 10 um); mobile phase: [Neu - MeOH]; B%: 60% - 60%, 7 min) to get the product 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide Isomer 1 (251.52 mg, 465.73 umol, 21.66% yield) as white oil. MS (ESI) m/z 540.3 $[M+H]^+$.

[000278] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.12 (d, J=1.8 Hz, 1H), 7.02 (s, 1H), 6.98 - 6.91 (m, 1H), 5.17 - 4.94 (m, 1H), 4.61 (s, 1H), 3.95 - 3.85 (m, 1H), 3.85 - 3.76 (m, 3H), 3.70 (br d, J=10.4 Hz, 1H), 3.29 - 3.13 (m, 2H), 2.64 - 2.23 (m, 3H), 2.09 - 1.87 (m, 2H), 1.82 - 1.68 (m, 2H), 1.64 - 1.39 (m, 12H).

[000279] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.05 (br s, 1H), 8.72 (br d, J=7.5 Hz, 1H), 7.28 (br s, 1H), 7.12 (br s, 1H), 6.97 (s, 2H), 4.97 (br s, 1H), 4.60 (br s, 1H), 3.80 (s, 4H), 3.61 (br s, 1H), 3.08 - 3.03 (m, 1H), 2.49 - 2.47 (m, 1H), 2.45 - 2.08 (m, 3H), 2.00 - 1.62 (m, 4H), 1.59 - 1.32 (m, 12H).

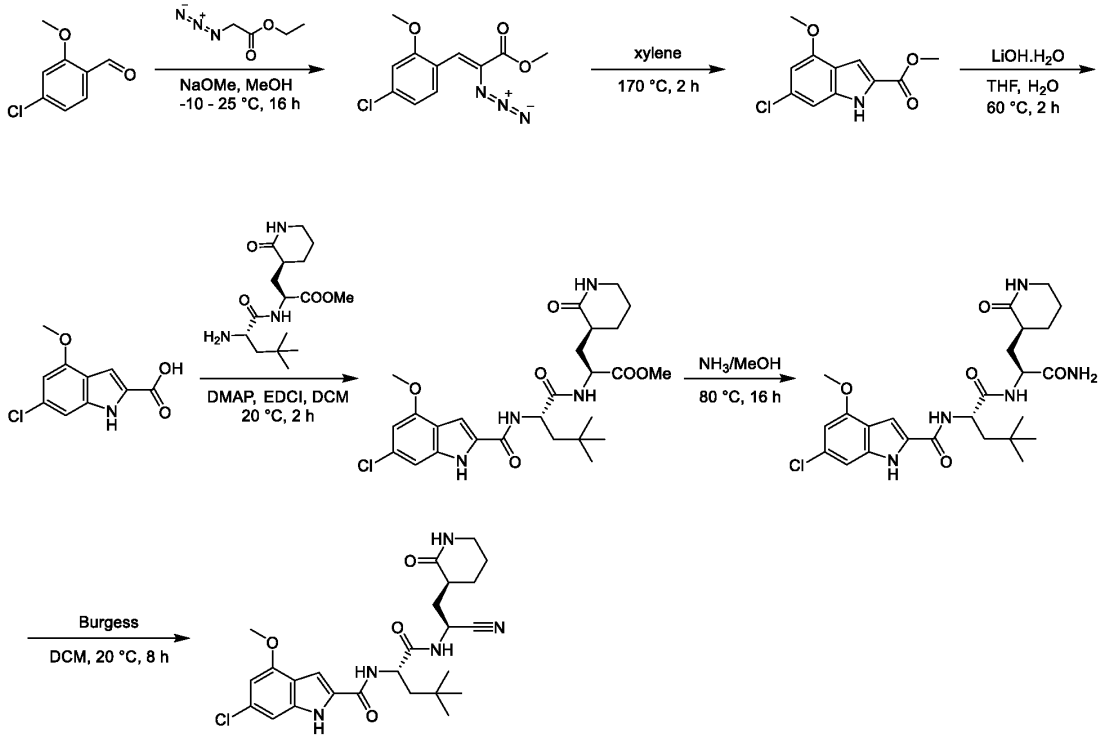
[000280] To get the product 2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide Isomer

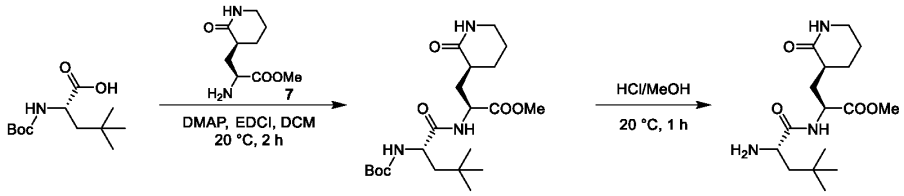
2 (366.62 mg, 678.86 umol, 31.57% yield) as white solid. MS (ESI) m/z 540.3 $[M+H]^+$.

[000281] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.01 (br s, 1H), 8.67 (br s, 1H), 7.25 (br s, 1H), 7.20 - 7.09 (m, 1H), 6.98 (s, 2H), 4.98 (br d, J = 7.1 Hz, 1H), 4.59 (br s, 1H), 3.80 (s, 4H), 3.62 (br s, 1H), 3.12 - 3.10 (m, 1H), 3.08 - 3.06 (m, 1H), 2.50 - 2.47 (m, 2H), 2.20 (br s, 3H), 1.83 (br s, 2H), 1.67 (br d, J = 11.5 Hz, 2H), 1.57 - 1.33 (m, 12H).

[000282] ^{1}H NMR (400 MHz, MeOD-d_4) δ = 7.13 (d, J = 2.1 Hz, 1H), 7.04 (s, 1H), 7.00 - 6.93 (m, 1H), 5.01 (dd, J = 6.2, 10.2 Hz, 1H), 4.62 (dd, J = 7.8, 9.8 Hz, 1H), 3.94 (br d, J = 10.4 Hz, 1H), 3.84 - 3.72 (m, 4H), 3.23 - 3.02 (m, 2H), 2.45 - 2.22 (m, 3H), 2.04 - 1.85 (m, 2H), 1.84 - 1.68 (m, 2H), 1.65 - 1.50 (m, 7H), 1.44 (br d, J = 10.1 Hz, 5H).

Example 282. Synthesis of viral protease inhibitor compound 1149





Step 1: (Z)-methyl 2-azido-3-(4-chloro-2-methoxyphenyl)acrylate

[000283] A mixture of NaOMe (6.33 g, 117.24 mmol, 2 eq) in MeOH (150 mL) was cooled to -10°C, and then a mixture of 4-chloro-2-methoxy-benzaldehyde (10 g, 58.62 mmol, 1 eq) and ethyl 2-azidoacetate (15.14 g, 117.24 mmol, 13.40 mL, 2 eq) in MeOH (150 mL) were added drop-wise to the former solution. The mixture was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated under the reduced pressure to give a residue and then quenched by addition H_2O (100 mL), and then extracted with EA (30 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO_2, PE:EA = 1:0 to 5:1) affording methyl(*Z*)-2-azido-3-(4-chloro-2-methoxy-phenyl)prop-2-enoate (8 g, 29.89 mmol, 50.99% yield) as a yellow solid.

Step 2: methyl 6-chloro-4-methoxy-1H-indole-2-carboxylate

[000284] Methyl (*Z*)-2-azido-3-(4-chloro-2-methoxy-phenyl) prop-2-enoate (7.60 g, 28.40 mmol, 1 eq) in xylene (80 mL) was stirred at 170 °C for 2 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The crude product was triturated with PE (10 mL) at 0 °C for 20 min affording methyl 6-chloro-4-methoxy-1*H*-indole-2-carboxylate (4 g, 16.69 mmol, 58.77% yield) as a white solid. MS (ESI) *m/z* 240.1 $[M+H]^+$

Step 3: (S)-methyl2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000285] To a solution of (2*S*)-2-(tert-butoxycarbonylamino)-4, 4-dimethyl-pentanoic acid (1 g, 4.08 mmol, 1 eq) and methyl (2*S*)-2-amino-3-[(3*S*)-2-oxo-3-piperidyl] propanoate (1.16 g, 4.89 mmol, 1.2 eq, HCl) in DCM (20 mL) was added DMAP (996.01 mg, 8.15 mmol, 2 eq) and EDCI (1.56 g, 8.15 mmol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by

addition H_2O (30 mL), and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give methyl(2*S*)-2-[[(2*S*)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (1 g, crude) as a yellow solid. MS (ESI) *m/z* 428.3 $[M+H]^+$

Step 4: (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000286] Methyl(2*S*)-2-[[(2*S*)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (1 g, 2.34 mmol, 1 eq) was added with HCl/MeOH (4 M, 10 mL, 17.10 eq), and then the mixture was stirred at 20 °C for 1 h. Upon completion, the mixture was concentrated under the reduced pressure to give methyl (2*S*)-2-[[(2*S*)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (0.8 g, crude, HCl) as a yellow solid. MS (ESI) *m/z* 328.2 $[M+H]^+$

Step 5: 6-chloro-4-methoxy-1H-indole-2-carboxylic acid

[000287] A mixture of methyl 6-chloro-4-methoxy-1*H*-indole-2-carboxylate (4 g, 16.69 mmol, 1 eq) in THF (30 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (2.10 g, 50.07 mmol, 3 eq). The mixture was stirred at 60 °C for 2 h. Upon completion, the mixture was quenched by addition H_2O (50 mL), and then added aq. HCl (1 M) to adjust the pH = 3-4, and extracted with EA (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-chloro-4-methoxy-1*H*-indole-2-carboxylic acid (4 g, crude) as a yellow solid. MS (ESI) *m/z* 226.0 $[M+H]^+$

Step 6: (S)-methyl2-((S)-2-(6-chloro-4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000288] To a mixture of methyl(2S)-2-[[(2S)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.8 g, 2.20 mmol, 1 eq, HCl) and 6-chloro-4-methoxy-1*H*-indole-2-carboxylic acid (744.08 mg, 3.30 mmol, 1.5 eq) in DCM (20 mL) was added DMAP (537.18 mg, 4.40 mmol, 2 eq) and EDCI (842.93 mg, 4.40 mmol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL), and then extracted with DCM (30

mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, PE:EA = 10:1 to 0:1) to give methyl(2*S*)-2-[[(2*S*)-2-[(6-chloro-4-methoxy-1*H*-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (1 g, 1.87 mmol, 85.01% yield) as a white solid. MS (ESI) *m/z* 535.2 $[M+H]^+$

Step 7: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-6-chloro-4-methoxy-1H-indole-2-carboxamide

[000289] Methyl(2*S*)-2-[[(2*S*)-2-[(6-chloro-4-methoxy-1*H*-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3*S*)-2-oxo-3-piperidyl]propanoate (1 g, 1.87 mmol, 1 eq) in NH_3/MeOH (7 M, 15 mL, 56.18 eq) was stirred at 80 °C for 16 h. Upon completion, the mixture was concentrated under the reduced pressure to give *N*-[(1*S*)-1-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-6- chloro-4-methoxy-1*H*-indole-2-carboxamide (0.8 g, crude) as a white solid. MS (ESI) *m/z* 520.2 $[M+H]^+$

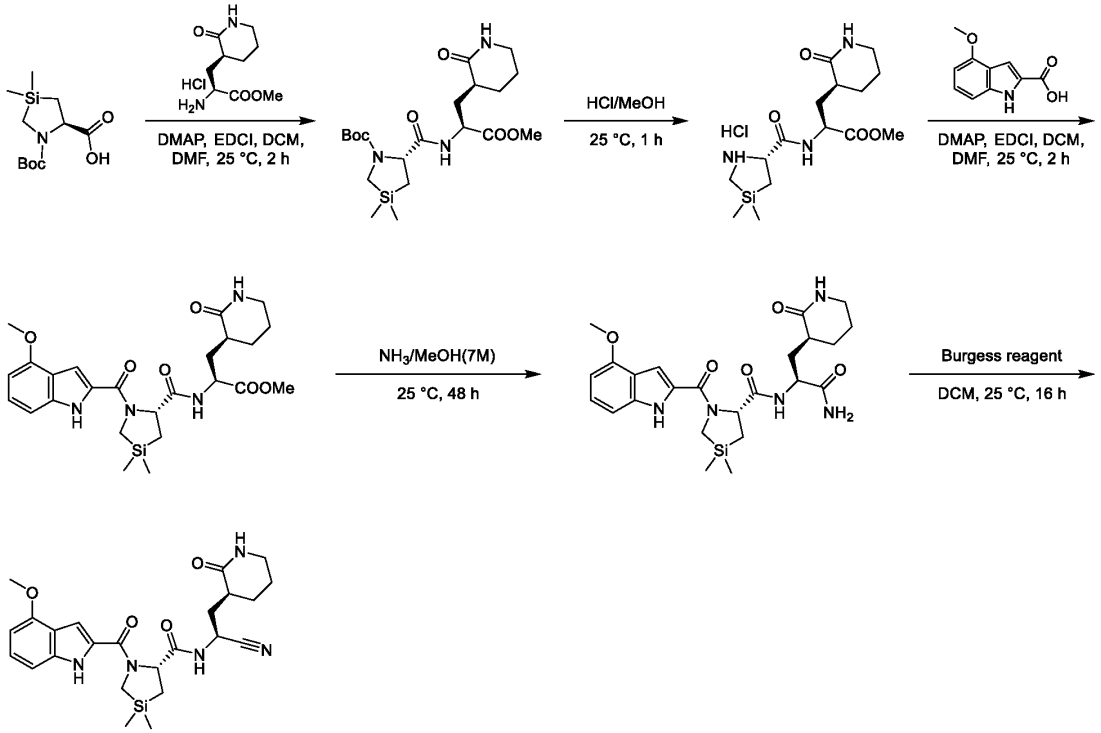
Step 8: 6-chloro-N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000290] To a solution of *N*-[(1*S*)-1-[[(1*S*)-2-amino-2-oxo-1-[[(3*S*)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-6-chloro-4-methoxy-1*H*-indole-2-carboxamide (700 mg, 1.35 mmol, 1 eq) in DCM (10 mL) was added burgess reagent (962.35 mg, 4.04 mmol, 3 eq). The mixture was stirred at 20 °C for 8 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 35% - 65%, 8 min) to give 6-chloro-*N*-[(1*S*)-1-[[(1*S*)-1-cyano-2-[(3*S*)-2-oxo-3-piperidyl]ethyl]carbamoyl]-3,3-dimethyl-butyl]-4-methoxy-1*H*-indole-2-carboxamide (230 mg, 458.16 umol, 34.04% yield, 100% purity) as a white solid. MS (ESI) *m/z* 502.1 $[M+H]^+$

[000291] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.72 (br s, 1H), 8.88 (d, *J* = 8.2 Hz, 1H), 8.53 (br d, *J* = 7.8 Hz, 1H), 7.51 (br s, 1H), 7.35 (s, 1H), 7.04 (s, 1H), 6.55 (d, *J* = 1.6 Hz, 1H), 5.14 - 4.93 (m, 1H), 4.51 - 4.48 (m, 1H), 3.91 (s, 3H), 3.16 - 2.99 (m, 2H),

2.32 - 2.17 (m, 2H), 1.88 - 1.73 (m, 3H), 1.71 - 1.62 (m, 2H), 1.59 - 1.46 (m, 1H), 1.44 - 1.31 (m, 1H), 0.93 (s, 9H)

Example 283. Synthesis of viral protease inhibitor compound 1151



Step 1: tert-butyl (5R)-5-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-1,3-azasilolidine-1-carboxylate

[000292] To a mixture of (5R)-1-tert-butoxycarbonyl-3,3-dimethyl-1,3-azasilolidine-5-carboxylic acid (300 mg, 1.16 mmol, 1 *eq*) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (301.15 mg, 1.27 mmol, 1.1 *eq*, HCl) in DCM (6 mL) and DMF (2 mL) was added DMAP (423.91 mg, 3.47 mmol, 3 *eq*) and EDCI (443.46 mg, 2.31 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was diluted with H_2O 22 mL and extracted with EA 45 mL (15 mL * 3). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 0/1) to give tert-butyl (5R)-5-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-1,3-

azasilolidine-1-carboxylate (500 mg, 1.13 mmol, 97.89% yield) as a yellow oil. (ESI) *m/z* 442.3 $[M+H]^+$

Step 2: methyl (2S)-2-[[(5R)-3,3-dimethyl-1,3-azasilolidine-5-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000293] A mixture of tert-butyl (5R)-5-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-3,3-dimethyl-1,3-azasilolidine-1-carboxylate (500 mg, 1.13 mmol, 1 *eq*) in HCl/MeOH (5 mL) was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give methyl (2S)-2-[[(5R)-3,3-dimethyl-1,3-azasilolidine-5-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (420 mg, 1.11 mmol, 98.15% yield, HCl) as a white solid.

Step 3: methyl (2S)-2-[[(5R)-1-(4-methoxy-1H-indole-2-carbonyl)-3,3-dimethyl-1,3-azasilolidine-5-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000294] To a mixture of 4-methoxy-1H-indole-2-carboxylic acid (193.15 mg, 1.01 mmol, 1 *eq*) and methyl (2S)-2-[[(5R)-3,3-dimethyl-1,3-azasilolidine-5-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.42 g, 1.11 mmol, 1.1 *eq*, HCl) in DCM (4 mL) and DMF (1 mL) was added DMAP (370.27 mg, 3.03 mmol, 3 *eq*) and EDCI (387.34 mg, 2.02 mmol, 2 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was diluted with H_2O 25 mL and extracted with EA 45 mL (15 mL * 3). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 0/1) to give methyl (2S)-2-[[(5R)-1-(4-methoxy-1H-indole-2-carbonyl)-3,3-dimethyl-1,3-azasilolidine-5-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (450 mg, 874.39 umol, 86.55% yield) as a yellow solid. (ESI) *m/z* 515.2 $[M+H]^+$

Step 4: (5R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-3,3-dimethyl-1,3-azasilolidine-5-carboxamide

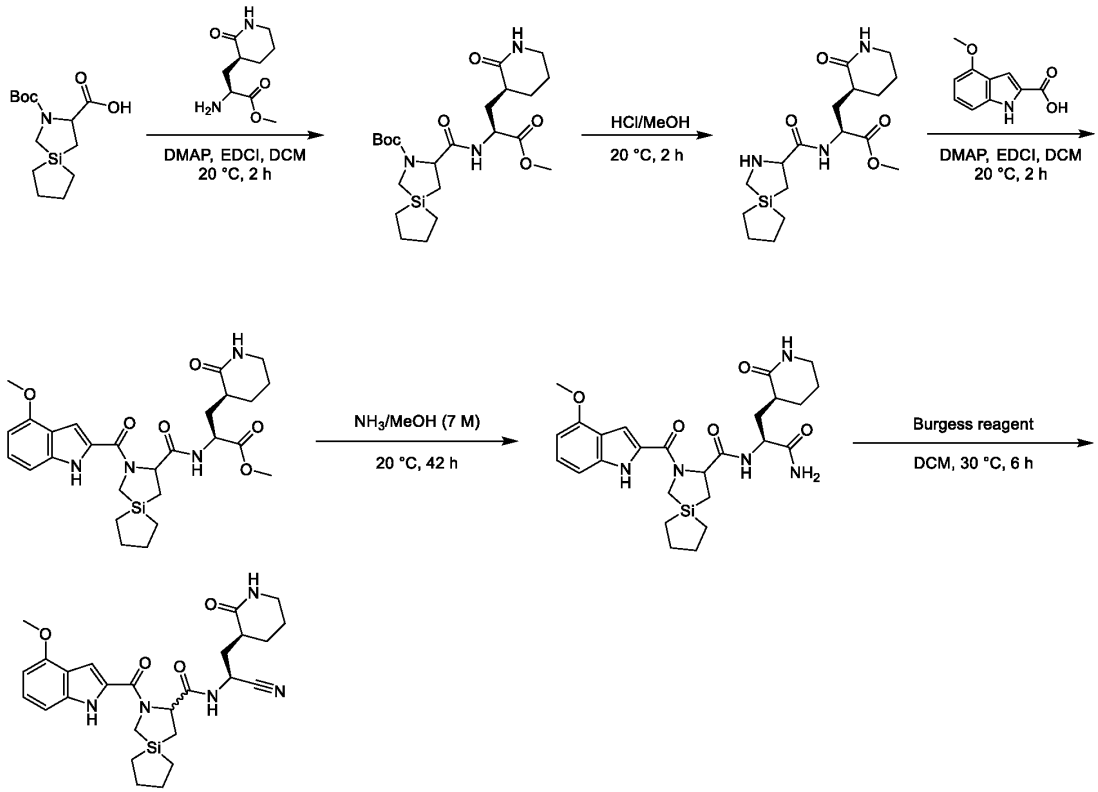
[000295] A mixture of methyl (2S)-2-[[(5R)-1-(4-methoxy-1H-indole-2-carbonyl)-3,3-dimethyl-1,3-azasilolidine-5-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (750 mg, 1.46 mmol, 1 *eq*) in NH_3/MeOH(7 M, 40 mL, 192.13 *eq*) was stirred at 25 °C for 48 h. Upon completion, the reaction mixture was concentrated under

reduced pressure to give (5R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-3,3-dimethyl-1,3-azasilolidine-5-carboxamide (720 mg, 1.44 mmol, 98.88% yield) as a yellow solid. MS (ESI) *m/z* 500.2 $[M+H]^+$

Step 5: (5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-3,3-dimethyl-1,3-azasilolidine-5-carboxamide

[000296] A mixture of (5R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-3,3-dimethyl-1,3-azasilolidine-5-carboxamide (640 mg, 922.28 umol, 72% purity, 1 *eq*) in DCM (10 mL) was added Burgess reagent (549.47 mg, 2.31 mmol, 2.5 *eq*) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude was purified by prep-HPLC (FA condition; column: Phenomenex Luna C18 200*40mm*10um;mobile phase: [water(0.2%FA)-ACN];B%: 35%-75%,8min) to give (5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-1-(4-methoxy-1H-indole-2-carbonyl)-3,3-dimethyl-1,3-azasilolidine-5-carboxamide (190 mg, 394.50 umol, 42.77% yield) as a yellow solid. MS (ESI) *m/z* 482.1 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.47 (br s, 1H), 8.78 (br d, *J* = 6.7 Hz, 1H), 7.52 (br s, 1H), 7.19 - 6.97 (m, 3H), 6.50 (d, *J* = 7.6 Hz, 1H), 5.01 (q, *J* = 7.9 Hz, 2H), 3.88 (br s, 3H), 3.35 (br s, 1H), 3.28 - 3.17 (m, 1H), 3.08 (br s, 2H), 2.31 - 2.10 (m, 2H), 1.99 - 1.47 (m, 4H), 1.44 - 1.16 (m, 2H), 0.98 (br d, *J* = 14.8 Hz, 1H), 0.33 - 0.15 (m, 6H)

Example 284. Synthesis of viral protease inhibitor compound 1153



Step 1: tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-aza-5-silaspiro[4.4]nonane-2-carboxylate

[000297] To a solution of 2-tert-butoxycarbonyl-2-aza-5-silaspiro[4.4]nonane-3-carboxylic acid (0.7 g, 2.45 mmol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (580.52 mg, 2.45 mmol, 1 eq, HCl) in DCM (8 mL) was added DMAP (898.90 mg, 7.36 mmol, 3 eq) and EDCI (940.33 mg, 4.91 mmol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL) and extracted with DCM (10 mL * 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 2:1 to 1:1 to 0:1) to give product tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-aza-5-silaspiro[4.4]nonane-2-carboxylate (0.8 g, 1.37 mmol, 55.80% yield, 80% purity) as yellow oil. MS (ESI) *m/z* 468.3 $[M+H]^+$

Step 2: methyl (2S)-2-(2-aza-5-silaspiro[4.4]nonane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000298] A solution of tert-butyl 3-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-2-aza-5-silaspiro[4.4]nonane-2-carboxylate (0.75 g, 1.28 mmol, 80% purity, 1 eq) in HCl/MeOH (4 M, 24.00 mL, 74.82 eq) was stirred at 20 °C for 2 h. Upon completion, the reaction was concentrated under pressure reduced to give crude product methyl (2S)-2-(2-aza-5-silaspiro[4.4]nonane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.5 g, crude, HCl) as yellow oil. MS (ESI) *m/z* 368.1 $[M+H]^+$

Step 3: methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate

[000299] To a solution of methyl (2S)-2-(2-aza-5-silaspiro[4.4]nonane-3-carbonylamino)-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.5 g, 1237.71 umol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (236.63 mg, 1237.71 umol, 1 eq) in DCM (10 mL) was added DMAP (453.63 mg, 1.49 mmol, 3 eq) and EDCI (474.53 mg, 1.49 mmol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction was quenched by addition H_2O (80 mL) and extracted with DCM (15 mL * 6). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 9/1 to 4/1 to1/1 to 0/1 and then Dichloromethane/Methanol = 10/1) to give the product methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.527 g, 274.89 umol, 89.59% yield, 85% purity) as yellow oil. MS (ESI) *m/z* 541.3 $[M+H]^+$

Step 4: N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carboxamide

[000300] A solution of methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.47 g, 869.27 umol, 1 eq) in NH_3/MeOH (1 mL, 7M) was stirred at 20 °C for 42 h. Upon completion, the reaction was concentrated under pressure reduced to get the crude product N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-

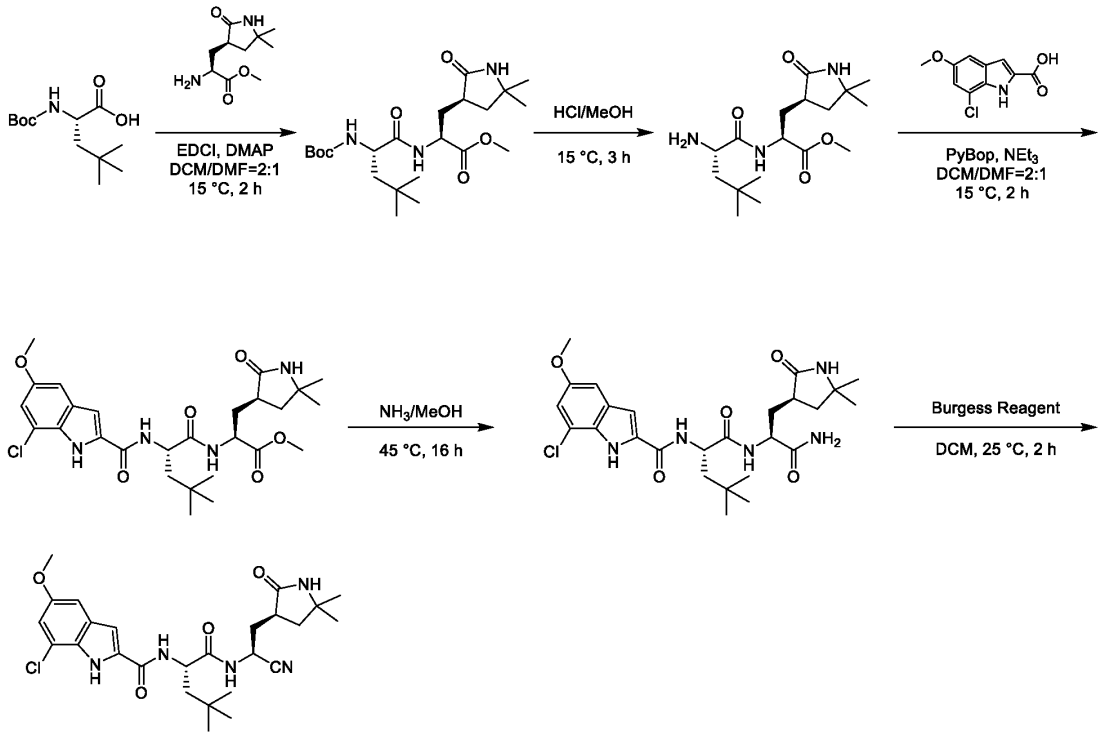
methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carboxamide (0.45 g, crude) as yellow solid. MS (ESI) *m/z* 526.3 $[M+H]^+$

Step 5: N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carboxamide

[000301] A solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carboxamide (0.46 g, 875.07 umol, 1 eq) in DCM (5 mL) was added burgess reagent (625.62 mg, 2.63 mmol, 3 eq). The mixture was stirred at 30 °C for 6 h. Upon completion, the mixture were quenched with water (3 mL) and blow-dried with N_2 and was purified by prep-HPLC (column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 35%-55%,10min) to give product N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carboxamide Isomer 1 (57 mg, 111.16 umol, 12.70% yield, 99% purity) as white solid. MS (ESI) *m/z* 508.1 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.52 (s, 1H), 8.86 (br d, *J* = 7.2 Hz, 1H), 7.51 (br s, 1H), 7.17 - 7.00 (m, 3H), 6.51 (d, *J* = 7.7 Hz, 1H), 5.00 - 4.99 (m, 1H), 5.09 - 4.94 (m, 1H), 3.88 (s, 3H), 3.51 - 3.42 (m, 1H), 3.08 (br s, 2H), 2.31 - 2.10 (m, 2H), 1.89 - 1.70 (m, 3H), 1.70 - 1.46 (m, 6H), 1.46 - 1.33 (m, 2H), 1.01 (br d, *J* = 15.2 Hz, 1H), 0.92 - 0.64 (m, 4H).

[000302] Get the product N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-2-(4-methoxy-1H-indole-2-carbonyl)-2-aza-5-silaspiro[4.4]nonane-3-carboxamide Isomer 2 (47 mg, 91.66 umol, 10.47% yield, 99% purity) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.48 (br s, 1H), 8.84 (br d, *J* = 7.3 Hz, 1H), 7.52 (br s, 1H), 7.19 - 7.00 (m, 3H), 6.50 (d, *J* = 7.7 Hz, 1H), 5.16 - 4.91 (m, 2H), 3.88 (s, 3H), 3.52 - 3.41 (m, 1H), 3.07 (br s, 2H), 2.31 - 2.19 (m, 2H), 1.88 - 1.73 (m, 2H), 1.72 - 1.46 (m, 7H), 1.45 - 1.32 (m, 2H), 1.11 - 0.99 (m, 1H), 0.91 - 0.70 (m, 4H).

Example 285. Synthesis of viral protease inhibitor compound 1163



Step 1: (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000303] To a solution of (S)-methyl 2-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (180.00 mg, 717.93 umol, 1 *eq*, HCl) in DMF (1 mL) and DCM (3 mL) was added DMAP (263.12 mg, 2.15 mmol, 3 *eq*), and then (S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanoic acid (211.34 mg, 865.51 umol, 1.2 *eq*) and EDCI (275.26 mg, 1.44 mmol, 2 *eq*) was added. The resulting solution was stirred at 15 °C for 2 h, and then diluted with water (10 mL) and extracted with DCM (5 mL * 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was used for next step directly. Compound (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (0.3 g, crude) was obtained as a yellow solid. MS (ESI) *m/z* 441.2 $[M+H]^+$.

Step 2 (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000304] A mixture of (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (0.28 g, 634.12 umol, 1 *eq*) in HCl/MeOH (4 mL) was stirred at 15 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (0.18 g, crude, HCl) as a yellow solid.

Step 3: (2S)-methyl 2-(2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carboxamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate

[000305] To a solution of (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (0.13 g, 380.74 umol, 1 *eq*, HCl) in DMF (0.7 mL) and DCM (1.3 mL) was added PyBop (198.13 mg, 380.71 umol, 1 *eq*), and then 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (85.90 mg, 380.71 umol, 1 *eq*) and NEt_3 (115.58 mg, 1.14 mmol, 3 *eq*) was added, the solution was stirred at 15 °C for 2 h. Upon completion, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 10:1 to 0:1) to give methyl (2S)-2-[[2-(4-methoxy-1H-indole-2-carbonyl)-8-oxa-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (0.16 g, 291.41 umol, 76.54% yield, 90% purity) as a white solid. MS (ESI) *m/z* 549.2 $[M+H]^+$.

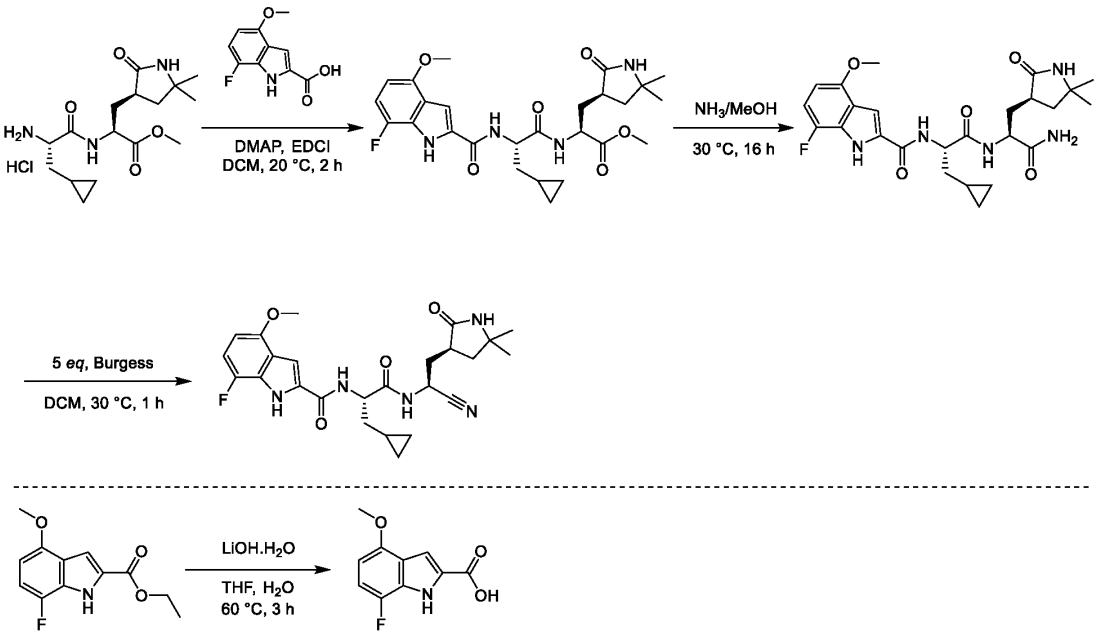
Step 4: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-5-methoxy-1H-indole-2-carboxamide

[000306] A mixture of (S)-methyl 2-((S)-2-(7-chloro-5-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (0.13 g, 246.88 umol, 1 *eq*) in NH_3.MeOH (7 M, 3 mL, 85.06 *eq*) was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-5-methoxy-1H-indole-2-carboxamide (0.12 g, crude) as a yellow oil. MS (ESI) *m/z* 534.2 $[M+H]^+$.

Step 5: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-5-methoxy-1H-indole-2-carboxamide

[000307] To a solution of N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-5-methoxy-1H-indole-2-carboxamide (0.11 g, 205.97 umol, 1 *eq*) in DCM (1 mL) was added burgess reagent (147.26 mg, 617.92 umol, 3 *eq*), and the solution was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was quenched with water (1 mL) and air dried. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN]) to give 7-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-5-methoxy-1H-indole-2-carboxamide (30.00 mg, 58.14 umol, 28.22% yield, 99% purity) as a white solid. MS (ESI) *m/z* 516.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.23 - 7.08 (m, 2H), 7.08 - 6.98 (m, 1H), 6.53 (br d, *J* = 7.6 Hz, 1H), 5.02 (br dd, *J* = 5.7, 10.1 Hz, 1H), 4.72 - 4.62 (m, 2H), 4.19 - 4.03 (m, 1H), 3.98 - 3.81 (m, 4H), 3.77 - 3.62 (m, 4H), 3.29 - 3.17 (m, 1H), 2.52 - 2.20 (m, 3H), 2.02 - 1.42 (m, 8H).

Example 286. Synthesis of viral protease inhibitor compound 1167



Step 1: 7-fluoro-4-methoxy-1H-indole-2-carboxylic acid

[000308] To a solution of ethyl 7-fluoro-4-methoxy-1*H*-indole-2-carboxylate (200 mg, 843.08 umol, 1 *eq*) in THF (4 mL) and H_2O (2 mL) was added $LiOH.H_2O$ (106.14 mg, 2.53 mmol, 3 *eq*), the mixture was stirred at 60 °C for 3 h. Upon the reaction completion, the mixture was concentrated in vacuum and was adjust pH~1 with 1M HCl (3 mL) and was extracted with EA (10 mL * 3), then was concentrated in vacuum to obtained 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid (170 mg, crude) as a white solid. MS (ESI) *m/z* 208.1 $[M-H]^+$

Step 2: (S)-methyl2-((S)-3-cyclopropyl-2-(7-fluoro-4-methoxy-1H-indole-2-carboxamido)propanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000309] To a solution of (*S*)-methyl2-((*S*)-2-amino-3-cyclopropylpropanamido)-3-((*R*)-5,5- dimethyl-2-oxopyrrolidin-3-yl)propanoate (150 mg, 414.52 umol, 1 *eq*, HCl) and 7-fluoro-4-methoxy-1*H*-indole-2-carboxylic acid (104.05 mg, 497.43 umol, 1.2 *eq*) in DCM (8 mL) was added DMAP (101.28 mg, 829.04 umol, 2 *eq*), then the mixture was added EDCI (158.93 mg, 829.04 umol, 2 *eq*), the mixture was stirred at 20 °C for 2 h. Upon the reaction completion, the mixture was filtered and was concentrated in vacuum and was purified by prep-TLC (SiO_2, EA = 1) to obtained (*S*)-methyl2-((*S*)-3-cyclopropyl-2-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido) propanamido)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl) propanoate (140 mg, 252.05 umol, 60.81% yield, 93% purity) as a yellow solid. MS (ESI) *m/z* 517.1 $[M+H]^+$

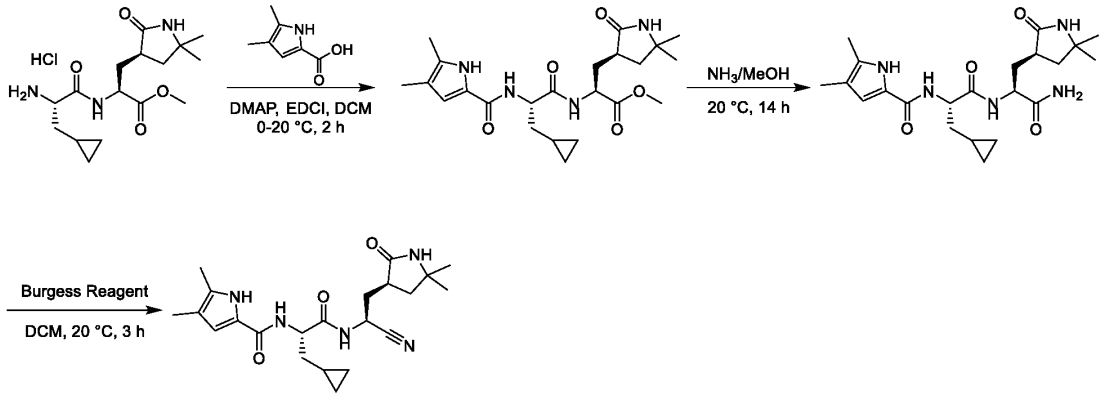
Step 3: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide

[000310] A solution of (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(7-fluoro-4-methoxy-1*H*-indole-2-carboxamido) propanamido)-3-((*R*)-5, 5-dimethyl-2-oxopyrrolidin-3-yl) propanoate (140 mg, 271.02 umol, 1 *eq*) in NH_3/MeOH (4 mL, 7M), the mixture was stirred at 30 °C for 16 h. Upon the reaction completion, the mixture was concentrated in vacuum to obtained *N*-((*S*)-1-(((*S*)-1-amino-3 -((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (130 mg, crude) as a yellow solid. MS (ESI) *m/z* 502.2 $[M+H]^+$

Step 4: N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide

[000311] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan -2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (120 mg, 239.26 umol, 1 *eq*) in DCM (6 mL) was added burgess reagent (285.09 mg, 1.20 mmol, 5 *eq*) at 30 °C, and then the resulting mixture was stirred at 30 °C for 1 h. Upon the reaction completion, the reaction mixture was quenched by water (1 mL) and was dried by blowing N_2 and was purified by prep-HPLC(column: Waters Xbridge C18 150 * 50mm * 10um; mobilephase: [water(10 mM NH_4HCO_3)-ACN]; B%: 25%-55%, 10min) to obtained *N*-((*S*)-1-(((*S*)-1-cyano-2-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl) ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (25 mg, 51.70 umol, 21.61% yield, 100% purity) as a white solid. MS (ESI) *m/z* 484.2$[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.14 - 11.90 (m, 1H), 9.03 - 8.85 (m, 1H), 8.54 (d, *J* = 7.4 Hz, 1H), 7.88 - 7.73 (m, 1H), 7.38 - 7.29 (m, 1H), 6.97 - 6.86 (m, 1H), 6.46 - 6.37 (m, 1H), 5.01 - 4.90 (m, 1H), 4.51 - 4.40 (m, 1H), 3.87 (s, 3H), 2.63 - 2.54 (m, 1H), 2.22 - 2.11 (m, 1H), 2.07 (s, 1H), 1.87 - 1.72 (m, 2H), 1.56 - 1.44 (m, 2H), 1.16 (s, 3H), 1.07 (s, 3H), 0.81 (s, 1H), 0.42 (d, *J* = 6.4 Hz, 2H), 0.24 - 0.16 (m, 1H), 0.10 (s, 1H).

Example 287. Synthesis of viral protease inhibitor compound 1173



Step 1: (S)-methyl 2-((S)-3-cyclopropyl-2-(4,5-dimethyl-1H-pyrrole-2-carboxamido)propanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000312] To a mixture of (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (140 mg, 340.46 umol, 88% purity, 1 *eq*, HCl) in DCM (3 mL) was added 4,5-dimethyl-1H-pyrrole-2-carboxylic acid (56.85 mg, 408.55 umol, 1.2 *eq*), and then then DMAP (124.78 mg, 1.02 mmol, 3 *eq*)

and EDCI (130.53 mg, 680.92 umol, 2 *eq*) were added at 0 °C. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition into water (3 mL), and then extracted with DCM (3 mL * 3). The combined organic layers were washed with HCl (1M, 3 mL), then washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give (S)-methyl 2-((S)-3-cyclopropyl-2-(4,5-dimethyl-1H-pyrrole-2-carboxamido)propanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (105 mg, 216.33 umol, 63.54% yield, 92% purity) as yellow solid. MS (ESI) *m/z* 447.1 $[M+H]^+$.

Step 2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,5-dimethyl-1H-pyrrole-2-carboxamide

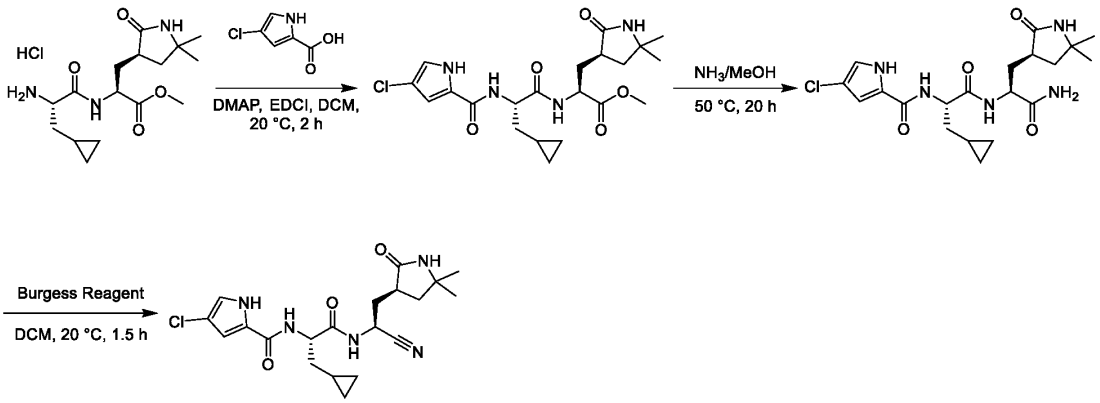
[000313] A mixture of (S)-methyl 2-((S)-3-cyclopropyl-2-(4,5-dimethyl-1H-pyrrole-2-carboxamido)propanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (100 mg, 206.03 umol, 92% purity, 1 *eq*) in NH_3/MeOH (7M, 5.48 mL, 186.06 *eq*) was stirred at 20 °C for 14 h. Upon completion, the reaction mixture was concentrated under reduced to give N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,5-dimethyl-1H-pyrrole-2-carboxamide (100 mg, crude) as white solid. MS (ESI) *m/z* 430.1 $[M-H]^+$.

Step 3: N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,5-dimethyl-1H-pyrrole-2-carboxamide

[000314] To a mixture of N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,5-dimethyl-1H-pyrrole-2-carboxamide (90 mg, 177.28 umol, 85% purity, 1 *eq*) in DCM (1 mL) was added burgess reagent (92.94 mg, 390.01 umol, 2.2 *eq*) and stirred at 20 °C for 14 h. Upon completion, the mixture was quenched with water (1 mL) and concentrated under reduced pressure to give a residue (<30 °C). The residue was purified by prep-HPLC (column:Phenomenex Luna C18 75*30mm*3um;mobile phase:[water(0.2%FA)-ACN];B%: 35%-65%,8min) to give N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,5-dimethyl-1H-pyrrole-2-carboxamide (4.27 mg, 10.12 umol, 5.71% yield, 98.0% purity) as white solid. MS (ESI) *m/z* 414.0 $[M+H]^+$. ^1H NMR (400 MHz,

DMSO-d_6) δ = 10.94 (br d, J = 1.5 Hz, 1H), 8.80 (d, J = 8.2 Hz, 1H), 7.81 (s, 1H), 7.77 - 7.71 (m, 1H), 6.61 (d, J = 2.6 Hz, 1H), 4.98 - 4.87 (m, 1H), 4.40 - 4.32 (m, 1H), 2.60 - 2.53 (m, 1H), 2.18 - 2.10 (m, 1H), 2.10 - 2.04 (m, 3H), 1.97 (dd, J = 8.6, 12.3 Hz, 1H), 1.90 (s, 3H), 1.80 - 1.69 (m, 2H), 1.53 - 1.44 (m, 1H), 1.43 - 1.35 (m, 1H), 1.19 - 1.12 (m, 3H), 1.06 (s, 3H), 0.80 - 0.67 (m, 1H), 0.45 - 0.31 (m, 2H), 0.18 - 0.00 (m, 2H).

Example 288. Synthesis of viral protease inhibitor compound 1175



Step 1: (S)-methyl 2-((S)-2-(4-chloro-1H-pyrrole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000315] To a mixture of (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (150 mg, 364.78 umol, 88% purity, 1 *eq*, HCl) in DCM (3 mL) was added 4-chloro-1H-pyrrole-2-carboxylic acid (63.71 mg, 437.73 umol, 1.2 *eq*). Then, HOBT (98.58 mg, 729.56 umol, 2 *eq*), DIEA (94.29 mg, 729.56 umol, 127.08 uL, 2 *eq*) and EDCI (139.86 mg, 729.56 umol, 2 *eq*) were added at 0 °C. The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition of water (3 mL), and then extracted with DCM (3 mL * 3). The combined organic layers were washed with HCl (1M, 3 mL), then washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give (S)-methyl 2-((S)-2-(4-chloro-1H-pyrrole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (110 mg, 242.86 umol, 66.58% yield) as yellow solid. MS (ESI) *m/z* 451.0 $[M-H]^+$.

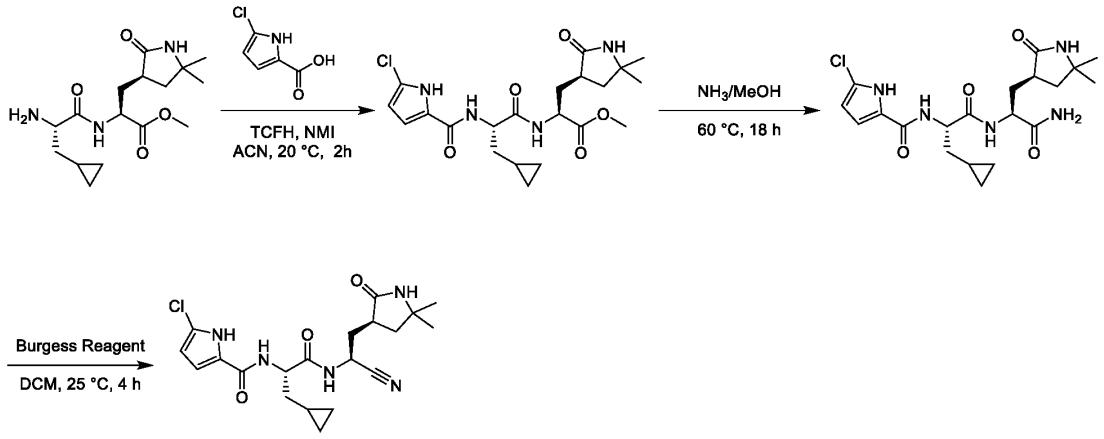
Step 2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-chloro-1H-pyrrole-2-carboxamide

[000316] A mixture of (S)-methyl 2-((S)-2-(4-chloro-1H-pyrrole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (100 mg, 220.78 umol, 100% purity, 1 *eq*) in NH_3/MeOH (7M, 3 mL, 95.12 *eq*) was stirred at 50 °C for 20 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-chloro-1H-pyrrole-2-carboxamide (95 mg, crude) as white solid. MS (ESI) *m/z* 438.2 $[M+H]^+$.

Step 3: 4-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrole-2-carboxamide

[000317] To a mixture of N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4-chloro-1H-pyrrole-2-carboxamide (95 mg, 190.90 umol, 88% purity, 1 *eq*) in DCM (1 mL) was added burgess reagent (136.48 mg, 572.71 umol, 3 *eq*) and stirred at 20 °C for 1.5 h. Upon completion, the reaction mixture was quenched with water (1 mL) and concentrated under reduced pressure to give a residue (<30 °C). The residue was purified by prep-HPLC(column:Waters Xbridge BEH C18 100*30mm*10um;mobile phase:[water(10mM NH_4HCO_3)-ACN];B%: 25%-55%,10min) to give 4-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrole-2-carboxamide (28.63 mg, 68.18 umol, 35.72% yield, 100% purity) as white solid. MS (ESI) *m/z* 420.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.84 - 11.68 (m, 1H), 8.88 (d, *J* = 8.2 Hz, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 7.83 (s, 1H), 6.95 (br d, *J* = 7.3 Hz, 2H), 5.01 - 4.86 (m, 1H), 4.46 - 4.29 (m, 1H), 2.62 - 2.53 (m, 1H), 2.19 - 2.09 (m, 1H), 2.03 - 1.92 (m, 1H), 1.81 - 1.71 (m, 2H), 1.54 - 1.36 (m, 2H), 1.16 (s, 3H), 1.10 - 0.99 (m, 3H), 0.83 - 0.69 (m, 1H), 0.47 - 0.33 (m, 2H), 0.21 - 0.02 (m, 2H).

Example 289. Synthesis of viral protease inhibitor compound 1177



Step 1: (S)-methyl 2-((S)-2-(5-chloro-1H-pyrrole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000318] To a solution of (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (150.00 mg, 460.97 umol, 1 *eq*, HCl) in ACN (5 mL) was added NMI (113.54 mg, 1.38 mmol, 3 *eq*), and then 5-chloro-1H-pyrrole-2-carboxpuriylic acid (67.09 mg, 460.97 umol, 1.0 *eq*) and TCFH (129.34 mg, 460.97 umol, 1 *eq*) was added, the solution was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was diluted with water (10 mL), extracted with EtOAc (5 mL * 3) and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Phenomenex Luna 80*30mm*3um; mobile phase: [water(0.1%TFA)-ACN]). Compound (S)-methyl 2-((S)-2-(5-chloro-1H-pyrrole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (60.0 mg, 132.37 umol, 28.74% yield, 90% purity) was obtained as a white solid. MS (ESI) *m/z* 453.2 $[M+H]^+$.

Step 2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-chloro-1H-pyrrole-2-carboxamide

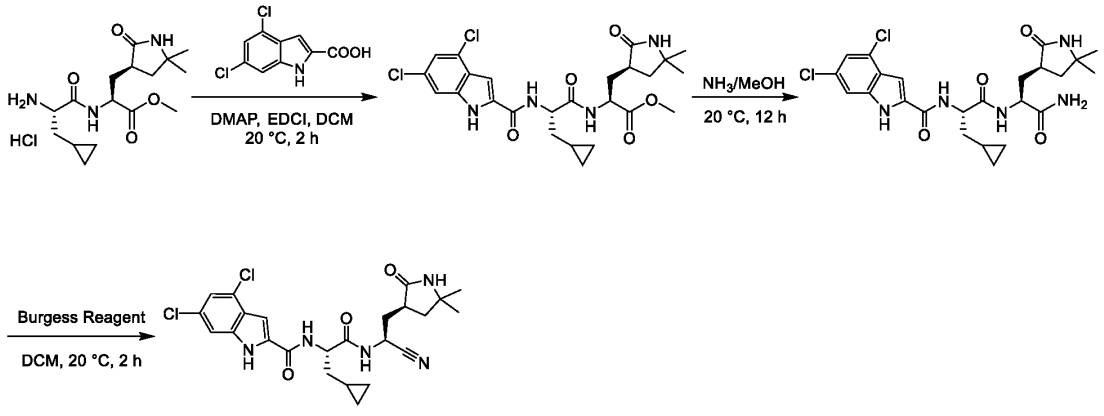
[000319] A mixture of (S)-methyl 2-((S)-2-(5-chloro-1H-pyrrole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5, 5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (60.00 mg, 132.47 umol, 1 *eq*) in HCl/MeOH (4 M, 4 mL) was stirred at 60 °C for 18 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-

2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-chloro-1H-pyrrole-2-carboxamide (50.00 mg, crude) as a white solid.

Step 3: 5-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrole-2-carboxamide

[000320] To a solution of N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-chloro-1H-pyrrole-2-carboxamide (50.00 mg, 114.18 umol, 1 *eq*) in DCM (1 mL) was added burgess reagent (81.63 mg, 342.53 umol, 3 *eq*), and then the solution was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was quenched with water (1 mL) and air dried. The residue was purified by prep-HPLC (Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water(10mM NH_4HCO_3)-ACN]) to give 5-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-pyrrole-2-carboxamide (5.00 mg, 11.91 umol, 10.43% yield) as a white solid. MS (ESI) *m/z* 420.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ ppm 6.82 (d, *J*=3.81 Hz, 1 H) 6.03 (d, *J*=3.93 Hz, 1 H) 5.01 (dd, *J*=10.37, 5.72 Hz, 1 H) 4.45 (t, *J*=7.39 Hz, 1 H) 2.87 - 2.71 (m, 1 H) 2.34 (ddd, *J*=13.77, 10.43, 5.13 Hz, 1 H) 2.14 (dd, *J*=12.40, 8.46 Hz, 1 H) 1.94 - 1.76 (m, 2 H) 1.65 - 1.53 (m, 2 H) 1.25 (s, 3 H) 1.16 (s, 3 H) 0.87 - 0.72 (m, 1 H) 0.51 (d, *J*=8.11 Hz, 2 H) 0.22 - 0.10 (m, 2 H)

Example 290. Synthesis of viral protease inhibitor compound 1181



Step 1: (S)-methyl 2-((S)-3-cyclopropyl-2-(4,6-dichloro-1H-indole-2-carboxamido)propanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000321] To a mixture of (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (140 mg, 386.89 umol, 1 *eq*, HCl) in DCM (3 mL) was added 4,6-dichloro-1H-indole-2-carboxylic acid (89.00 mg, 386.89 umol, 1 *eq*), DMAP (141.80 mg, 1.16 mmol, 3 *eq*) and EDCI (148.33 mg, 773.77 umol, 2 *eq*), then stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition of water (3 mL), and then extracted with DCM (5 mL * 3). The combined organic layers were washed with HCl (1M, 5 mL), then washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO2, DCM: MeOH = 10:1). To give (S)-methyl 2-((S)-3-cyclopropyl-2-(4,6-dichloro-1H-indole-2-carboxamido)propanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (130 mg, 241.89 umol, 62.52% yield) as yellow solid. MS (ESI) *m/z* 537.2 $[M+H]^+$.

Step 2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,6-dichloro-1H-indole-2-carboxamide

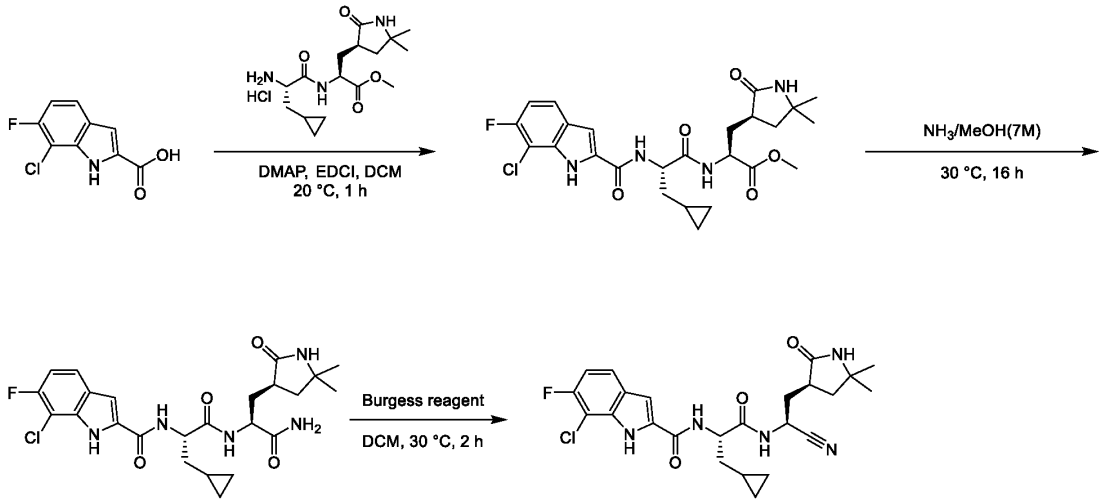
[000322] To a mixture of (S)-methyl 2-((S)-3-cyclopropyl-2-(4,6-dichloro-1H-indole-2-carboxamido)propanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (110 mg, 204.68 umol, 1 *eq*) in HN_3/MeOH (7 M, 2 mL, 68.40 *eq*) was stirred at 80 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,6-dichloro-1H-indole-2-carboxamide (110 mg, crude) as white solid. MS (ESI) *m/z* 522.2 $[M+H]^+$.

Step 3: 4,6-dichloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-indole-2-carboxamide

[000323] To a mixture of N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-4,6-dichloro-1H-indole-2-carboxamide (105 mg, 180.89 umol, 90% purity, 1 *eq*) in DCM (2 mL) was added burgess reagent (258.64 mg, 1.09 mmol, 6 *eq*) then stirred at 20 °C for 2 h. Upon completion, the mixture was quenched with water (0.1 mL) and concentrated under reduced pressure to give a residue(<30 °C). The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100* 30 mm* 10 um; mobile phase:

[water(10 mM NH_4HCO_3)- ACN]; B%: 35%-65%, 8 min) to give 4,6-dichloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-1H-indole-2-carboxamide as white solid. MS (ESI) *m/z* 504.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.99 - 11.77 (m, 1H), 8.84 - 8.66 (m, 1H), 8.60 - 8.49 (m, 1H), 7.55 - 7.35 (m, 2H), 7.40 - 7.32 (m, 1H), 7.19 (d, *J* = 1.5 Hz, 1H), 5.03 - 4.88 (m, 1H), 4.64 - 4.45 (m, 1H), 2.60 - 2.54 (m, 1H), 2.28 - 2.14 (m, 1H), 2.12 - 1.99 (m, 1H), 1.90 - 1.75 (m, 2H), 1.66 - 1.51 (m, 2H), 1.22 - 1.09 (m, 6H), 0.91 - 0.73 (m, 1H), 0.48 - 0.39 (m, 2H), 0.28 - 0.03 (m, 2H)

Example 291. Synthesis of viral protease inhibitor compound 1191



Step1: methyl (2S)-2-[[(2S)-2-[(7-chloro-6-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[000324] To a mixture of 7-chloro-6-fluoro-1H-indole-2-carboxylic acid (0.1 g, 374.54 umol, 80% purity, 1.2 eq) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (112.94 mg, 312.12 umol, 1 eq, HCl) in DCM (3 mL) were added EDCI (119.67 mg, 624.24 umol, 2 eq) and DMAP (114.40 mg, 936.36 umol, 3 eq), and then the resulting mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (20 mL) and extracted with DCM (6 mL * 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give

methyl (2S)-2-[[(2S)-2-[(7-chloro-6-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (0.14 g, 241.85 umol, 77.49% yield, 90% purity) as white solid. MS (ESI) *m/z* 521.2 $[M+H]^+$

Step2: N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-6-fluoro-1H-indole-2-carboxamide

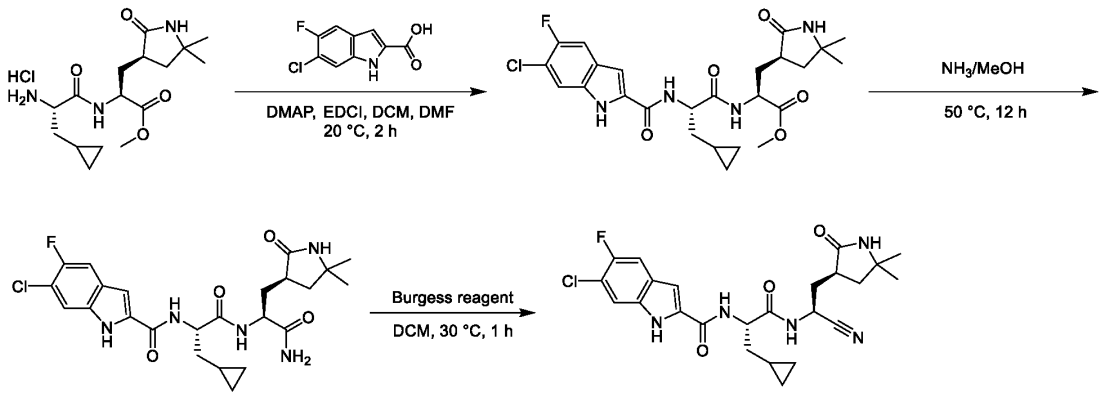
[000325] A solution of methyl (2S)-2-[[(2S)-2-[(7-chloro-6-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (0.12 g, 230.34 umol, 1 eq) in NH_3/MeOH (3 mL) was stirred at 30 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to get the crude product N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-6-fluoro-1H-indole-2-carboxamide (0.11 g, crude) as white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$

Step3: 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-fluoro-1H-indole-2-carboxamide

[000326] To a solution of N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-7-chloro-6-fluoro-1H-indole-2-carboxamide (0.11 g, 173.92 umol, 80% purity, 1 eq) in DCM (3 mL) was added burgess reagent (82.90 mg, 347.85 umol, 2 eq), the mixture was stirred at 30 °C for 2 h. Upon completion, the mixture were quenched with water (1 mL) and blow-dried with N_2 and was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-60%,8min) to give the product 7-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-fluoro-1H-indole-2-carboxamide (0.058 g, 118.86 umol, 68.34% yield, 100% purity) as white solid. MS (ESI) *m/z* 488.1 $[M+H]^+$ ^1H NMR (400MHz, DMSO-d_6) δ = 11.89 (br s, 1H), 9.01 (d, J = 7.9 Hz, 1H), 8.69 (d, J = 7.5 Hz, 1H), 7.83 (s, 1H), 7.66 (dd, J = 4.8, 8.7 Hz, 1H), 7.27 (s, 1H), 7.13 (dd, J = 8.9, 10.0 Hz, 1H), 4.97 (br d, J = 7.9 Hz, 1H), 4.50 (br d, J = 6.6 Hz, 1H), 2.63 - 2.55 (m, 1H), 2.26 - 2.09 (m, 1H),

2.00 (dd, J = 8.4, 12.2 Hz, 1H), 1.90 - 1.72 (m, 2H), 1.59 - 1.44 (m, 2H), 1.15 (s, 3H), 1.07 (s, 3H), 0.90 - 0.75 (m, 1H), 0.55 - 0.35 (m, 2H), 0.25 - 0.16 (m, 1H), 0.15 - 0.07 (m, 1H).

Example 292. Synthesis of viral protease inhibitor compound 1193



Step1: methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[000327] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (0.1 g, 276.35 umol, 1 eq, HCl) and 6-chloro-5-fluoro-1H-indole-2-carboxylic acid (70.83 mg, 331.62 umol, 1.2 eq) in DCM (3 mL), DMF (0.5 mL) was added EDCI (105.95 mg, 552.70 umol, 2 eq), DMAP (101.28 mg, 829.04 umol, 3 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL) and extracted with DCM (8 mL * 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give product methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (0.08 g, 141.27 umol, 51.12% yield, 92% purity) as white solid. MS (ESI) *m/z* 521.2 $[M+H]^+$

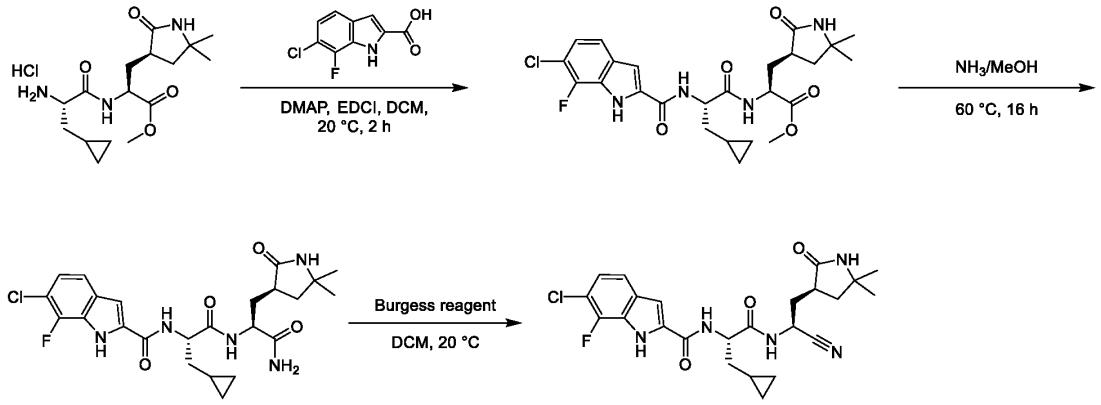
Step2: N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro-1H-indole-2-carboxamide

[000328] The methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (0.07 g, 134.36 umol, 1 eq) in NH_3/MeOH (1 mL) was stirred at 50 °C for 12 h. Upon completion, the reaction mixture was concentrated under pressure reduced to get the crude product N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro-1H-indole-2-carboxamide (0.05 g, crude) as white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$

Step3: 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide

[000329] The solution of N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro-1H-indole-2-carboxamide (0.03 g, 56.33 umol, 95% purity, 1 eq) in DCM (1 mL) was added burgess reagent (53.69 mg, 225.31 umol, 4 eq). The mixture was stirred at 30 °C for 1 h. Upon completion, the mixture were quenched with water (1 mL) and blow-dried with N_2, and was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-65%,8min) to give the product 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-1H-indole-2-carboxamide (0.017 g, 34.84 umol, 61.85% yield, 100% purity) as a white solid. MS (ESI) *m/z* 488.1 $[M+H]^+$ ^1H NMR (400MHz, DMSO-d_6) δ = 7.52 (d, J = 6.4 Hz, 1H), 7.46 - 7.42 (m, 1H), 7.17 (d, J = 0.7 Hz, 1H), 5.04 (dd, J = 5.7, 10.5 Hz, 1H), 4.54 (t, J = 7.5 Hz, 1H), 2.92 - 2.77 (m, 1H), 2.40 - 2.31 (m, 1H), 2.21 - 2.11 (m, 1H), 1.88 (br s, 2H), 1.71 - 1.55 (m, 2H), 1.26 - 1.23 (m, 3H), 1.14 (s, 3H), 0.91 - 0.77 (m, 1H), 0.59 - 0.46 (m, 2H), 0.19 (dd, J = 5.0, 10.6 Hz, 2H)

Example 293. Synthesis of viral protease inhibitor compound 1195



Step 1: (S)-methyl 2-((S)-2-(6-chloro-7-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000330] To a mixture of (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (140 mg, 344.19 umol, 80% purity, 1 *eq*) in DCM (3 mL) was added 6-chloro-7-fluoro-1H-indole-2-carboxylic acid (88.22 mg, 413.03 umol, 1.2 *eq*), DMAP (126.15 mg, 1.03 mmol, 3 *eq*) and EDCI (131.96 mg, 688.38 umol, 2 *eq*), then the resulting mixture stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition of water (1 mL), and then extracted with DCM (3 mL * 3). The combined organic layers were washed with HCl (1M, 3 mL), then washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO2, DCM:MeOH = 10:1) to give (S)-methyl 2-((S)-2-(6-chloro-7-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (140 mg, 241.85 umol, 70.27% yield, 90% purity) as yellow solid. MS (ESI) *m/z* 519.0 $[M-H]^+$.

Step 2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-chloro-7-fluoro-1H-indole-2-carboxamide

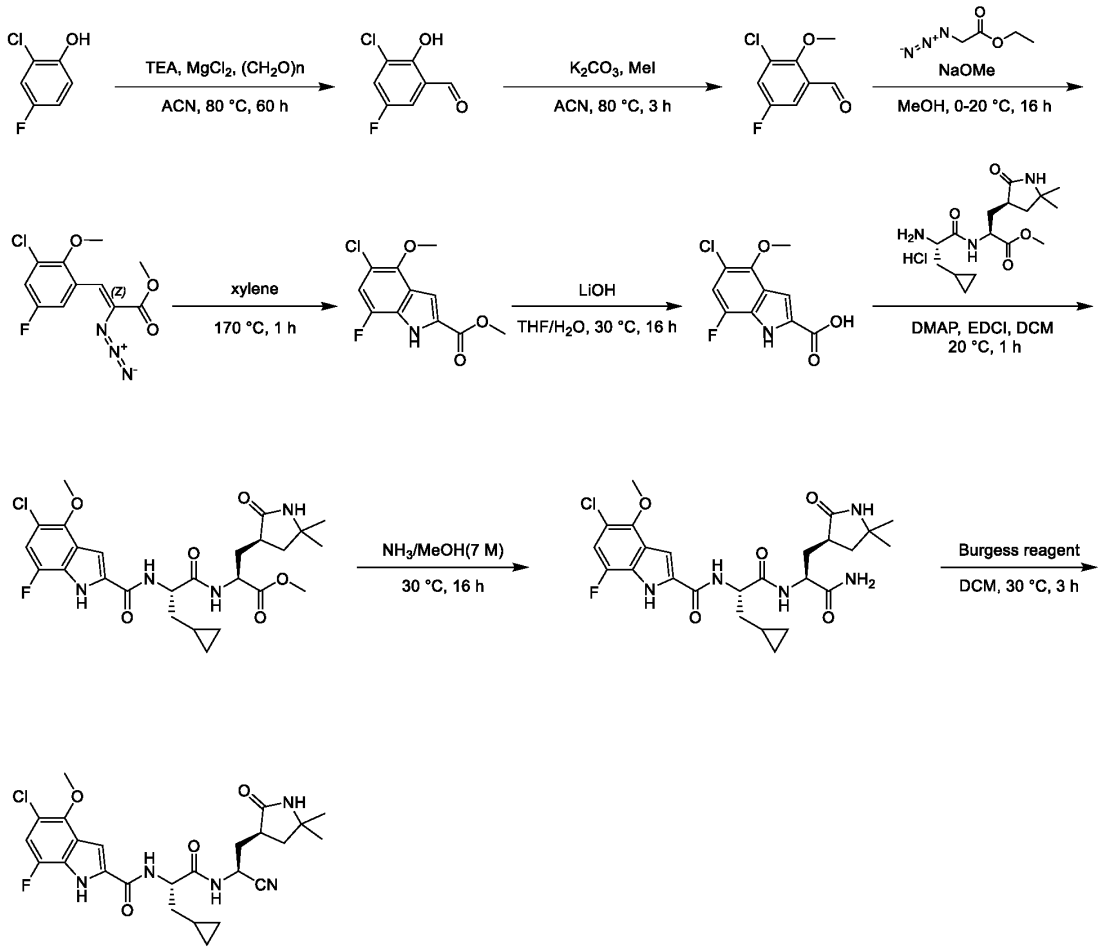
[000331] To a mixture of (S)-methyl 2-((S)-2-(6-chloro-7-fluoro-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (140 mg, 241.85 umol, 90% purity, 1 *eq*) in NH_3/MeOH (7 M, 3 mL, 86.83 *eq*) was stirred at 60 °C for 16 h. Upon completion, The reaction mixture was concentrated under reduced pressure to give N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-

oxopropan-2-yl)-6-chloro-7-fluoro-1H-indole-2-carboxamide (140 mg, crude) as white solid. MS (ESI) *m/z* 504.0 $[M-H]^+$.

Step 3: 6-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-1H-indole-2-carboxamide

[000332] To a mixture of N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-chloro-7-fluoro-1H-indole-2-carboxamide (130 mg, 205.55 umol, 80% purity, 1 *eq*) in DCM (2 mL) was added burgess reagent (146.95 mg, 616.64 umol, 3 *eq*), then stirred at 20 °C for 2 h. Upon completion, the mixture was quenched with water (1 mL) and concentrated under reduced pressure to give a residue (<30 °C). The residue was purified by prep-HPLC(column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 35%-65%, 10 min) to give 6-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-1H-indole-2-carboxamide (29.53 mg, 60.09 umol, 29.24% yield, 99.3% purity) as white solid. MS (ESI) *m/z* 488.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 12.35 - 12.19 (m, 1H), 8.99 (d, *J* = 7.9 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 7.83 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.32 (d, *J* = 3.1 Hz, 1H), 7.13 (dd, *J* = 6.4, 8.6 Hz, 1H), 5.02 - 4.90 (m, 1H), 4.53 - 4.42 (m, 1H), 2.61 - 2.54 (m, 1H), 2.22 - 2.11 (m, 1H), 1.99 (dd, *J* = 8.4, 12.1 Hz, 1H), 1.89 - 1.72 (m, 2H), 1.57 - 1.42 (m, 2H), 1.18 - 1.03 (m, 6H), 0.88 - 0.73 (m, 1H), 0.50 - 0.34 (m, 2H), 0.26 - 0.03 (m, 2H)

Example 294. Synthesis of viral protease inhibitor compound 1201



Step 1: 3-chloro-5-fluoro-2-hydroxybenzaldehyde

[000333] To a solution of 2-chloro-4-fluoro-phenol (5 g, 34.12 mmol, 1 *eq*) and $MgCl_2$ (9.80 g, 102.93 mmol, 4.22 mL, 3.02 *eq*) in ACN (300 mL) was added TEA (9.45 g, 93.40 mmol, 13.00 mL, 2.74 *eq*), (HCHO)n (3.5 g, 34.12 mmol, 1.00 *eq*), the mixture was stirred at 80 °C for 60 h. Upon the reaction completion, the mixture was concentrated in vacuum and acidified with aqueous HCl (100 mL, 3M) solution to pH~1, and extracted with EtOAc (50 mL * 3), then the organic phase was concentrated in vacuum and purified by column (SiO_2, PE = 1) to obtained 3-chloro-5-fluoro-2- hydroxybenzaldehyde (5 g, 25.21 mmol, 73.88% yield, 88% purity) as a yellow solid. MS (ESI) *m/z* 173.1 $[M-H]^+$

Step 2: 3-chloro-5-fluoro-2-methoxybenzaldehyde

[000334] To a solution of 3-chloro-5-fluoro-2-hydroxybenzaldehyde (1 g, 5.73 mmol, 1 *eq*) in ACN (20 mL) was added K_2CO_3 (2.38 g, 17.19 mmol, 3 *eq*) and CH_3I (1.30 g, 9.17 mmol, 570.62 uL, 1.6 *eq*), the mixture was stirred at 80 °C for 3 h. Upon the reaction completion, the mixture was concentrated in vacuum and was added water (60 mL) and was extracted with DCM (20 mL * 3), then was dried with Na_2SO_4, filtered and concentrated in vacuum to obtained 3-chloro-5-fluoro-2-methoxybenzaldehyde (1 g, crude) as a yellow oil. MS (ESI) *m/z* 189.1 $[M+H]^+$

Step 3: (Z)-methyl 2-azido-3-(3-chloro-5-fluoro-2-methoxyphenyl)acrylate

[000335] To a solution of NaOMe (572.94 mg, 10.61 mmol, 2 *eq*) in MeOH (20 mL) was added a solution of 3-chloro-5-fluoro-2-methoxybenzaldehyde (1 g, 5.30 mmol, 1 *eq*) and ethyl 2-azidoacetate (1.37 g, 10.61 mmol, 1.21 mL, 2 *eq*) in MeOH (10 mL) at 0 °C. The mixture was stirred at 20 °C for 16 h. Upon the reaction completion, the mixture was concentrated in vacuum and was added water (60 mL) and extracted with EtOAc (30 mL * 3), then was concentrated in vacuum and was purified by column (SiO_2, PE:EA = 1:0 to 50:1) to obtained (*Z*)-methyl 2-azido-3-(3-chloro-5-fluoro-2-methoxyphenyl) acrylate (0.35 g, 1.05 mmol, 19.81% yield) as a yellow solid.

Step 4: methyl 5-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxylate

[000336] A solution of (*Z*)-methyl 2-azido-3-(3-chloro-5-fluoro-2-methoxyphenyl) acrylate (350.00 mg, 1.23 mmol, 1 *eq*) in xylene (5 mL) was stirred at 170 °C for 1 h. Upon the reaction completion, the mixture was concentrated in vacuum to obtained methyl 5-chloro-7-fluoro-4-methoxy-1*H*-indole-2-carboxylate (300 mg, crude) as a yellow solid.

Step 5: 5-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxylic acid

[000337] To a solution of methyl 5-chloro-7-fluoro-4-methoxy-1*H*-indole-2-carboxylate (300 mg, 1.16 mmol, 1 *eq*) in THF (2 mL) and H_2O (2 mL) was added $LiOH.H_2O$ (146.59 mg, 3.49 mmol, 3 *eq*), the mixture was stirred at 30 °C for 16 h. Upon the reaction completion, the mixture was concentrated in vacuum and was adjusted pH~1 with aqueous HCl (15 mL, 1M), then was extracted with EtOAc (5 mL * 3), then was concentrated in vacuum to obtained 5-chloro-7-fluoro-4-methoxy-1*H*-indole-2 - carboxylic acid (250 mg, crude) as a yellow solid. MS (ESI) *m/z* 189.1 $[M+H]^+$

Step 6: (S)-methyl2-((S)-2-(5-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000338] To a solution of methyl (2*S*)-2-[[(2*S*)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3*R*)-5,5- dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (250 mg, 690.87 umol, 1 *eq*, HCl) and 5-chloro-7-fluoro-4-methoxy-1*H*-indole-2 -carboxylic acid (168.31 mg, 690.87 umol, 1 *eq*) in DCM (5 mL) was added DMAP (253.21 mg, 2.07 mmol, 3 *eq*) and EDCI (264.88 mg, 1.38 mmol, 2 *eq*), and then the resulting mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was adjusted pH~1 with 1M HCl (3 mL) and was added water (6 mL), then was extracted with DCM (3 mL * 3), then the organic phase was dried with Na_2SO_4, the mixture was concentrated in vacuum and was purified by prep-TLC (SiO_2, EtOAc = 1) to obtained (*S*)-methyl2-((*S*)-2-(5-chloro-7-fluoro-4-methoxy-1*H*-indole-2- carboxamido)-3-cyclopropylpropanamido)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl) propanoate (180 mg, 294.01 umol, 42.56% yield, 90% purity) as a white solid. MS (ESI) *m/z* 551.2 $[M+H]^+$

Step 7: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxamide

[000339] A solution of (*S*)-methyl 2-((*S*)-2-(5-chloro-7-fluoro-4-methoxy-1*H*-indole-2-carboxamido) -3-cyclopropylpropanamido)-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl) propanoate (160 mg, 290.38 umol, 1 *eq*) in NH_3/MeOH (8 mL, 7M) was stirred at 30 °C for 16 h. Upon the reaction completion, the mixture was concentrated in vacuum to obtained *N*-((*S*)-1-(((*S*)-1-amino-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-chloro-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (100 mg, crude) as a yellow solid. MS (ESI) *m/z* 536.1 $[M+H]^+$

Step 8: 5-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide

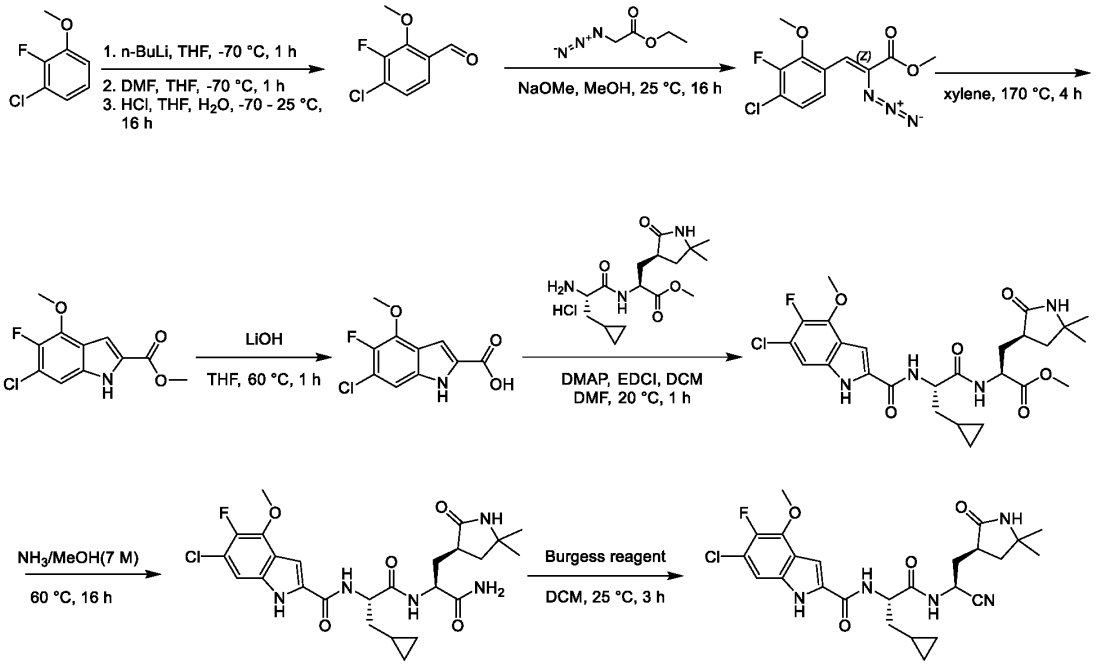
[000340] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-3-((*R*)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan -2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-chloro-7-fluoro-4-

methoxy-1*H*-indole-2-carboxamide (90 mg, 167.91 umol, 1 *eq*) in DCM (2 mL) was added burgess reagent (120.05 mg, 503.74 umol, 3 *eq*) at 30 °C, and then the resulting mixture was stirred at 30 °C for 3 h. Upon the reaction completion, the mixture was quenched by water (0.5 mL) and was dried by blowing N_2 and was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 35%-70%, 10 min) to obtained 5-chloro-*N*-((*S*)-1-(((*S*)-1-cyano-2-((*R*)-5,5-dimethyl-2- oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1*H*-indole-2-carboxamide (15 mg, 28.88 umol, 17.20% yield, 99.74% purity) as a white solid. MS (ESI) *m/z* 518.1 $[M+H]^+$

[000341] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.36 (s, 1H), 9.07 - 8.91 (m, 1H), 8.76 - 8.63 (m, 1H), 7.84 - 7.79 (m, 1H), 7.70 - 7.32 (m, 1H), 7.17 (d, *J* = 10.4 Hz, 1H), 4.97 (q, *J* = 8.2 Hz, 1H), 4.53 - 4.43 (m, 1H), 4.03 - 3.77 (m, 3H), 2.61 - 2.54 (m, 1H), 2.21 - 2.12 (m, 1H), 2.05 - 1.96 (m, 1H), 1.89 - 1.73 (m, 2H), 1.57 - 1.43 (m, 2H), 1.19 - 1.13 (m, 3H), 1.10 - 1.04 (m, 3H), 0.87 - 0.76 (m, 1H), 0.48 - 0.38 (m, 2H), 0.24 - 0.07 (m, 2H).

[000342] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ ppm 12.05 (s, 1H), 8.71 (d, *J* = 7.8 Hz, 1H), 8.44 - 8.33 (m, 1H), 7.56 - 7.49 (m, 1H), 7.44 - 7.35 (m, 1H), 7.09 (d, *J* = 10.4 Hz, 1H), 5.00 - 4.93 (m, 1H), 4.60 - 4.53 (m, 1H), 4.04 - 3.81 (m, 3H), 2.63 - 2.55 (m, 1H), 2.25 - 2.16 (m, 1H), 2.14 - 2.06 (m, 1H), 1.90 - 1.75 (m, 2H), 1.69 - 1.52 (m, 2H), 1.23 - 1.17 (m, 3H), 1.16 - 1.11 (m, 3H), 0.88 - 0.79 (m, 1H), 0.50 - 0.42 (m, 2H), 0.24 - 0.09 (m, 2H).

Example 295. Synthesis of viral protease inhibitor compound 1203



Step 1: 4-chloro-3-fluoro-2-methoxy-benzaldehyde

[000343] To a mixture of 1-chloro-2-fluoro-3-methoxy-benzene (5 g, 31.14 mmol, 1 *eq*) in THF (100 mL) was added n-BuLi (2.5 M, 13.70 mL, 1.1 *eq*) in one portion at -70 °C under N_2. The mixture was stirred at -70 °C for 1 h, then added DMF (18.66 g, 255.35 mmol, 19.65 mL, 8.2 *eq*) in THF (35 mL) at -70 °C, and then the resulting mixture was stirred at -70 °C for 1 h, then HCl (1 M, 75 mL, 2.41 *eq*) was added and heated to 25 °C and stirred for 16 h. ~20% reactant was still, the reaction mixture was diluted with H_2O 100 mL and extracted with EA 200 mL (100 mL * 2). The combined organic layers were washed with BRINE 100 mL (100 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue.

[000344] The residue was purified by neutral prep-HPLC (column: Welch Xtimate C18 250*70mm#10um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 35%-65%, 20 min). Compound 4-chloro-3-fluoro-2-methoxy-benzaldehyde (1 g, 4.77 mmol, 15.33% yield, 90% purity) was obtained as a white solid. MS (ESI) *m/z* 189.0 $[M+H]^+$

Step2: methyl (Z)-2-azido-3-(4-chloro-3-fluoro-2-methoxy-phenyl)prop-2-enoate

[000345] To a mixture of NaOMe (229.18 mg, 4.24 mmol, 2 *eq*) in MeOH (8 mL) was cooled to -10 °C, a mixture 4-chloro-3-fluoro-2-methoxy-benzaldehyde (400 mg, 2.12

mmol, 1 *eq*) and ethyl 2-azidoacetate (547.73 mg, 4.24 mmol, 484.72 uL, 2 *eq*) in MeOH (4 mL) was dropwise to this solution. The mixture was stirred at 25 °C for 16 h and yellow solid was observed. Upon completion, the reaction mixture was filtered to give a residue. The residue was purified by prep-TLC (Petroleum ether:Ethyl acetate = 20:1). Compound methyl (Z)-2-azido-3-(4-chloro-3-fluoro-2-methoxy-phenyl) prop-2-enoate (200 mg, 630.12 umol, 29.71% yield, 90% purity) was obtained as a white solid.

Step 3: methyl 6-chloro-5-fluoro-4-methoxy-1H-indole-2-carboxylate

[000346] A solution of methyl (Z)-2-azido-3-(4-chloro-3-fluoro-2-methoxy-phenyl)prop-2-enoate (140 mg, 490.10 umol, 1 *eq*) in xylene (10 mL) was stirred at 170 °C for 4 h. ~10% reactant was still. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (Petroleum ether:Ethyl acetate = 2:1). Compound methyl 6-chloro-5-fluoro-4-methoxy-1H-indole-2-carboxylate (96 mg, 353.98 umol, 72.23% yield, 95% purity) was obtained as a white solid.

Step 4: 6-chloro-5-fluoro-4-methoxy-1H-indole-2-carboxylic acid

[000347] To a mixture of methyl 6-chloro-5-fluoro-4-methoxy-1H-indole-2-carboxylate (96 mg, 372.61 umol, 1 *eq*) in THF (2 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (31.27 mg, 745.21 umol, 2 *eq*). The mixture was stirred at 60 °C for 1 h. Upon completion, the reaction mixture was adjusted pH=3 by addition HCl, and then diluted with H_2O 30 mL and extracted with EA 100 mL (50 mL * 2). The combined organic layers were washed with brine 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was used next step directly. Compound 6-chloro-5-fluoro-4-methoxy-1H-indole-2-carboxylic acid (70 mg, crude) was obtained as a yellow solid. MS (ESI) *m/z* 241.9 $[M-H]^+$

Step 5: methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[000348] To a mixture of 6-chloro-5-fluoro-4-methoxy-1H-indole-2-carboxylic acid (70 mg, 287.33 umol, 1 *eq*) and methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (103.98 mg, 287.33 umol, 1 *eq*, HCl) in DCM (6 mL) and DMF (3 mL) was added DMAP

(70.21 mg, 574.67 umol, 2 *eq*) and EDCI (110.17 mg, 574.67 umol, 2 *eq*). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O 20 mL and extracted with EA 40 mL (20 mL * 2). The combined organic layers were washed with brine 20 mL (20 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1). Compound methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (120 mg, 206.89 umol, 72.00% yield, 95% purity) was obtained as a colourless oil. MS (ESI) *m/z* 551.1 $[M+H]^+$

Step 6: N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl] amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro-4-methoxy-1H-indole-2-carboxamide

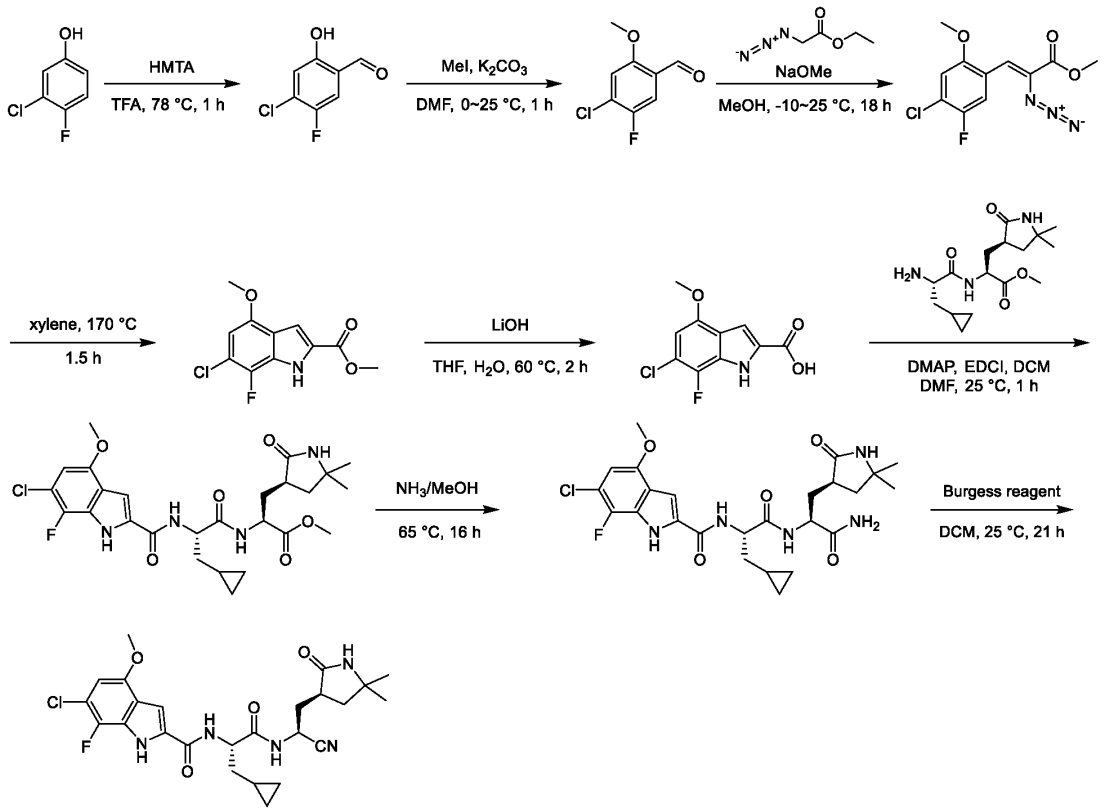
[000349] A solution of methyl (2S)-2-[[(2S)-2-[(6-chloro-5-fluoro-4-methoxy-1H-indole-2-carbonyl)amino]-3-cyclopropyl-propanoyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (100 mg, 181.49 umol, 1 *eq*) in NH_3/MeOH (7 M, 15.00 mL, 578.56 *eq*) was stirred at 60 °C for another 16 h. Upon completion, the reaction mixture concentrated under reduced pressure to give a residue and used next step directly. Compound N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro -4-methoxy-1H-indole-2-carboxamide (90 mg, crude) was obtained as a white solid. MS (ESI) *m/z* 536.2 $[M+H]^+$

Step 7: 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide

[000350] To a mixture of N-[(1S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-chloro-5-fluoro-4-methoxy-1H-indole-2-carboxamide (90 mg, 167.91 umol, 1 *eq*) in DCM (5 mL) was added burgess reagent (80.03 mg, 335.82 umol, 2 *eq*). The mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was diluted with H_2O 5 mL and extracted with DCM 10 mL (5 mL * 2). The combined organic layers

were concentrated by blow-drying to give a residue. The residue was purified by neutral prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 40%-70%, 10 min). Compound 6-chloro-N-[(1S)-2-[[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide (52 mg, 97.18 umol, 57.87% yield, 96.8% purity) was obtained as a white solid. MS (ESI) *m/z* 518.1 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ = 11.81 (br d, *J* = 1.1 Hz, 1H), 8.96 (d, *J* = 8.1 Hz, 1H), 8.69 (d, *J* = 7.6 Hz, 1H), 7.82 (s, 1H), 7.57 (d, *J* = 0.9 Hz, 1H), 7.26 - 7.16 (m, 1H), 5.05 - 4.88 (m, 1H), 4.54 - 4.40 (m, 1H), 4.12 (d, *J* = 1.3 Hz, 3H), 2.55 (br s, 1H), 2.23 - 2.11 (m, 1H), 1.98 (dd, *J* = 8.6, 12.3 Hz, 1H), 1.89 - 1.71 (m, 2H), 1.57 - 1.40 (m, 2H), 1.15 (s, 3H), 1.05 (s, 3H), 0.86 - 0.74 (m, 1H), 0.49 - 0.34 (m, 2H), 0.25 - 0.16 (m, 1H), 0.14 - 0.04 (m, 1H).

Example 296. Synthesis of viral protease inhibitor compound 1205



Step 1: (S)-methyl 2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000351] HMTA (5.00 g, 35.67 mmol, 1.05 *eq*) was added to TFA (80 mL) in small portions and the resulting mixture was heated to reflux at 78 °C. A solution of 3-chloro-4-fluorophenol (5 g, 34.12 mmol, 1 *eq*) in TFA (30 mL) was then added dropwise and the mixture was stirred for another 1 h. Upon completion, the mixture was cooled to room temperature and concentrated in vacuum. The residue was poured into ice-water (50 mL) and stirred overnight. The mixture was filtered and the filter cake dissolved in EA (50 mL), dried over Na_2SO_4 and concentrated in vacuum to give 4-chloro-5-fluoro-2-hydroxybenzaldehyde (5.5 g, crude) as yellow oil. MS (ESI) *m/z* 175.0 $[M+H]^+$.

Step 2: 4-chloro-5-fluoro-2-methoxybenzaldehyde

[000352] To a solution of 4-chloro-5-fluoro-2-hydroxybenzaldehyde (5.35 g, 15.32 mmol, 50% purity, 1 *eq*) in DMF (1 mL), was adeded K_2CO_3 (4.24 g, 30.65 mmol, 2 *eq*), then MeI (4.35 g, 30.65 mmol, 1.91 mL, 2 *eq*) was added dropwise at 0 °C, the mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure and the residue was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate=1:0 to 5:1) to give 4-chloro-5-fluoro-2-methoxybenzaldehyde (920 mg, 4.63 mmol, 30.24% yield, 95 % purity) as a yellow solid. MS (ESI) *m/z* 189.0 $[M+H]^+$.

Step 3: (Z)-methyl 2-azido-3-(4-chloro-5-fluoro-2-methoxyphenyl)acrylate

[000353] To a solution of NaOMe (515.61 mg, 9.54 mmol, 2 *eq*) in MeOH (10 mL), was added ethyl 2-azidoacetate (1.23 g, 9.54 mmol, 1.09 mL, 2 *eq*) and 4-chloro-5-fluoro-2-methoxybenzaldehyde (900 mg, 4.77 mmol, 1 *eq*) in MeOH (10 mL) dropwise at -10 °C. The mixture was stirred at 25 °C for 18 h. Upon completion, the reaction mixture was concentrated under reduced pressure and the residue was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM 150 mL (50 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over Na_2SO_4,

filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate=1:0 to 20:1) to give (Z)-methyl 2-azido-3-(4-chloro-5-fluoro-2-methoxyphenyl) acrylate (390 mg, 1.30 mmol, 27.18% yield, 95 % purity) as a yellow solid. MS (ESI) *m/z* 286.0 $[M+H]^+$.

Step 4: methyl 6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxylate

[000354] A solution of methyl (Z)-methyl 2-azido-3-(4-chloro-5-fluoro-2-methoxyphenyl)acrylate (390 mg, 1.37 mmol, 1 *eq*) in xylene (10 mL) was stirred at 170 °C for 1.5 h. Upon completion, the reaction mixture was cooled to 25 °C, solid precipitation, then filtration, the crude product was washed with PE 100 mL to give methyl 6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxylate (220 mg, 811.19 umol, 59.42% yield, 95% purity) as a white solid. MS (ESI) *m/z* 258.0 $[M+H]^+$.

Step 5: 6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxylic acid

[000355] To a solution of methyl 6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxylate (200 mg, 776.26 umol, 1 *eq*) in THF (2 mL) and H_2O (0.5 mL) was added $LiOH.H_2O$ (97.72 mg, 2.33 mmol, 3 *eq*), and then the resulting mixture was stirred at 60 °C for 2 h. Upon completion, the resulting solution was adjusted to pH~5 with 1 M HCl and then extracted with EtOAc (5 mL x 2). The combined organic phasewas dried over Na_2SO_4, filtered and concentrated to give 6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxylic acid (190 mg, crude) as a white solid. MS (ESI) *m/z* 244.0 $[M+H]^+$.

Step 6: (S)-methyl 2-((S)-2-(6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000356] To a solution of 6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxylic acid (190 mg, 779.91 umol, 1 *eq*) in DCM (2 mL) and DMF (2 mL) was added (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (416.92 mg, 1.01 mmol, 88% purity, 1.3 *eq*, HCl), DMAP (285.84 mg, 2.34 mmol, 3 *eq*) and EDCI (299.02 mg, 1.56 mmol, 2 *eq*), after the addition the mixture was stirred at 25 °C for 1 h. Upon completion, the resulting solution was poured into brine (10 mL), and then extracted with EtOAc (10 mL * 2), the combined organic layers washed with citric acid (20 mL * 2), then washed with $NaHCO_3$ (10 mL), brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated to give a crude

product. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1 to 0/1) to give (S)-methyl 2-((S)-2-(6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (210 mg, 381.12 umol, 48.87% yield) as a white solid. MS (ESI) *m/z* 551.2 $[M+H]^+$.

Step 7: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxamide

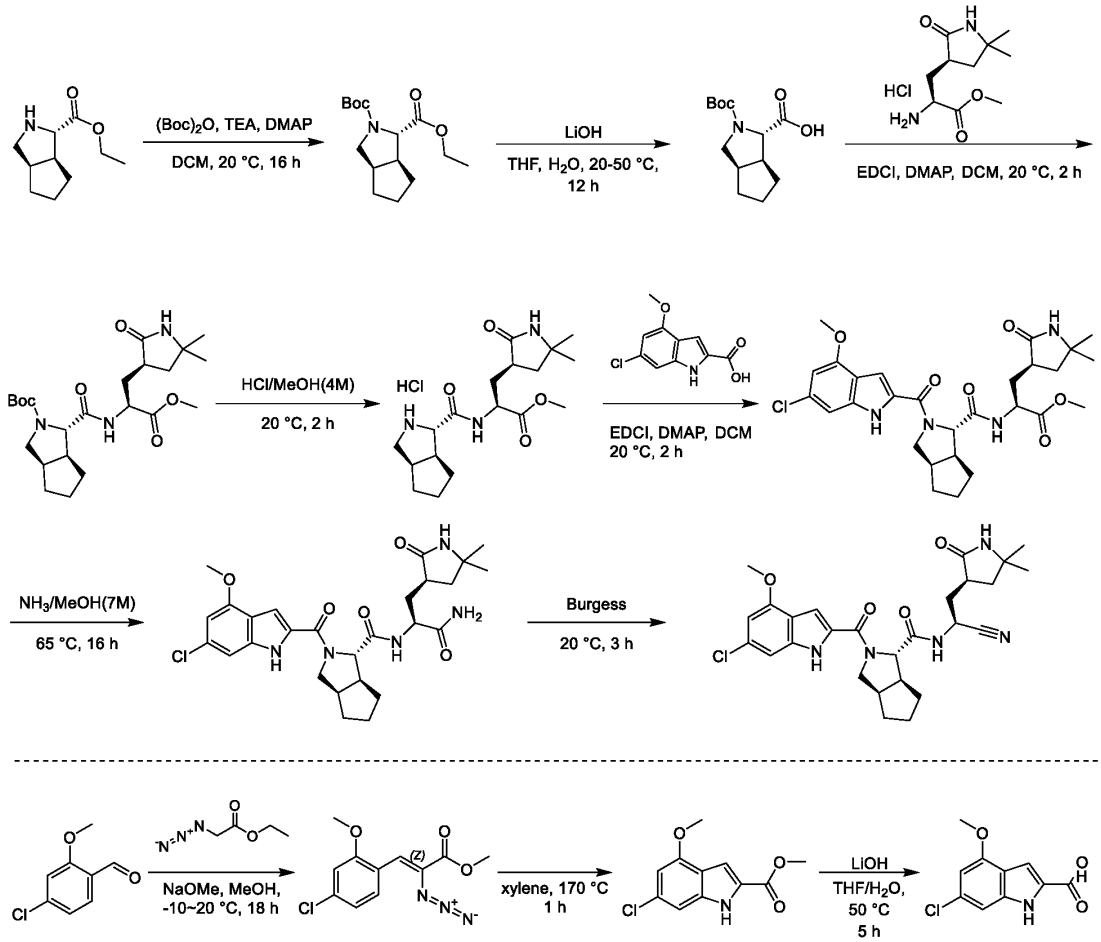
[000357] A solution of (S)-methyl 2-((S)-2-(6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxamido)-3-cyclopropylpropanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate (190 mg, 344.82 umol, 1 eq) in NH_3/MeOH (7 M, 3.83 mL, 77.66 eq) was stirred at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent to give N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxamide (186 mg, crude) as a white solid. MS (ESI) *m/z* 536.2 $[M+H]^+$.

Step 8: 6-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide

[000358] To a solution of N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-chloro-7-fluoro-4-methoxy-1H-indole-2-carboxamide (186 mg, 347.02 umol, 1 eq) in DCM (4 mL) was added Burgess reagent (165.40 mg, 694.04 umol, 2 eq), and then the mixture was stirred at 25 °C for 3 h. LCMS showed most starting material was remained, then was added Burgess reagent (82.70 mg, 347.02 umol, 1 eq) was stirred another 12 h. LCMS showed a little starting material was remained, then was added Burgess reagent (82.70 mg, 347.02 umol, 1 eq) and was stirred for another 6 h. Upon completion, the resulting solution was quenched with H_2O (0.5 mL), then was concentrated in vacuum (25°C). The residue was purified by prep-HPLC column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 30%-65%, 10 min to give 6-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-

3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-7-fluoro-4-methoxy-1H-indole-2-carboxamide (50.52 mg, 97.53 umol, 28.11% yield, 100% purity) as a white solid. MS (ESI) *m/z* 518.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) 8.94 (d, J = 8.2 Hz, 1H), 8.60 (d, J = 7.6 Hz, 1H), 7.82 (s, 1H), 7.37 (d, J = 2.8 Hz, 1H), 6.59 (d, J = 4.6 Hz, 1H), 5.04 - 4.88 (m, 1H), 4.54 - 4.35 (m, 1H), 3.89 (s, 3H), 2.61 - 2.53 (m, 1H), 2.21 - 2.12 (m, 1H), 1.99 (dd, J = 8.4, 12.3 Hz, 1H), 1.84 - 1.73 (m, 2H), 1.53 - 1.44 (m, 2H), 1.16 (s, 3H), 1.06 (s, 3H), 0.87 - 0.74 (m, 1H), 0.44 - 0.34 (m, 2H), 0.21 - 0.05 (m, 2H)

Example 297. Synthesis of viral protease inhibitor compound 1215



Step 1: (Z)-methyl 2-azido-3-(4-chloro-2-methoxyphenyl)acrylate

[000359] To a solution of NaOMe (9.50 g, 175.86 mmol, 2 *eq*) in MeOH (100 mL) was added 4-chloro-2-methoxy-benzaldehyde (15 g, 87.93 mmol, 1 *eq*) and ethyl 2-azidoacetate (23.84 g, 184.65 mmol, 21.10 mL, 2.1 *eq*) in MeOH (100 mL) at -10 °C. The mixture was stirred at 20 °C for 18 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 20 °C, and then concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 80/1) to give methyl (Z)-2-azido-3-(4-chloro-2-methoxy-phenyl)prop-2-enoate (15.5 g, 57.91 mmol, 65.86% yield) as a yellow solid.

Step 2: methyl 6-chloro-4-methoxy-1H-indole-2-carboxylate

[000360] A solution of methyl (Z)-2-azido-3-(4-chloro-2-methoxy-phenyl)prop-2-enoate (10 g, 37.36 mmol, 1 *eq*) in xylene (100 mL) was stirred at 170 °C for 2 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give methyl 6-chloro-4-methoxy-1H-indole-2-carboxylate (4 g, crude) as a white solid.

Step 3: 6-chloro-4-methoxy-1H-indole-2-carboxylic acid

[000361] To a solution of methyl 6-chloro-4-methoxy-1H-indole-2-carboxylate (4 g, 16.69 mmol, 1 *eq*) in THF (30 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (2.10 g, 50.07 mmol, 3 *eq*). The mixture was stirred at 50 °C for 5 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. 1M HCl was added, adjust pH to 3, then was filtered and concentrated under reduced pressure to give 6-chloro-4-methoxy-1H-indole-2-carboxylic acid (3.5 g, crude) as a white solid.

Step 4: (1S,3aR,6aS)-2-tert-butyl 1-ethyl hexahydrocyclopenta[c]pyrrole-1,2(1H)-dicarboxylate

[000362] To a solution of ethyl (3S,3aS,6aR)-1,2,3,3a,4,5,6,6a-octahydrocyclopenta[c]pyrrole-3-carboxylate (1.5 g, 8.19 mmol, 1 *eq*), TEA (993.96 mg, 9.82 mmol, 1.37 mL, 1.2 *eq*) in DCM (15 mL), was added $(Boc)_2O$ (2.14 g, 9.82 mmol, 2.26 mL, 1.2 *eq*), and then DMAP (200.01 mg, 1.64 mmol, 0.2 *eq*) was added. The mixture was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was poured into H_2O 30 mL at 20 °C, and then extracted with DCM (35 mL * 3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4,

filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 80/1) to give O2-tert-butyl O3-ethyl (3S,3aS,6aR)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2,3-dicarboxylate (2 g, 7.06 mmol, 86.22% yield) as a colorless oil.

Step 5: (1S,3aR,6aS)-2-(tert-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid

[000363] To a solution of O2-tert-butyl O3-ethyl (3S,3aS,6aR)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2,3-dicarboxylate (2 g, 7.06 mmol, 1 *eq*) in THF (15 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (888.55 mg, 21.17 mmol, 3 *eq*). The mixture was stirred at 50 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove solvent. 1M HCl was added, adjust pH to 3, and then filtered and concentrated under reduced pressure to give (3S,3aS,6aR)-2-tert-butoxycarbonyl-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carboxylic acid (1.7 g, crude) as a white solid.

Step 6: (1S,3aR,6aS)-tert-butyl 1-(((S)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate

[000364] To a solution of (3S,3aS,6aR)-2-tert-butoxycarbonyl-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carboxylic acid (534.61 mg, 2.09 mmol, 1.5 *eq*), methyl (2S)-2-amino-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (350 mg, 1.40 mmol, 1 *eq*, HCl) in DCM (7 mL) was added DMAP (426.36 mg, 3.49 mmol, 2.5 *eq*), and then EDCI (535.22 mg, 2.79 mmol, 2 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O 15 mL at 20 °C, and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (15 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 60/1 to 40/1) to give tert-butyl (3S,3aS,6aR)-3-[[(1S)-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carboxylate (600 mg, 1.20 mmol, 85.67% yield, 90% purity) as a yellow solid.

Step 7: (S)-methyl 3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-2-((1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxamido)propanoate

[000365] A solution of tert-butyl (3S,3aS,6aR)-3-[[(1S)-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-methoxy-2-oxo-ethyl]carbamoyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-2-carboxylate (550 mg, 1.22 mmol, 1 *eq*) in HCl/MeOH (10 mL) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove MeOH to give methyl (2S)-2-[[(3S,3aS,6aR)-1,2,3,3a,4,5,6,6a-octahydrocyclopenta[c]pyrrole-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (472 mg, crude, HCl) as a yellow solid.

Step 8: (S)-methyl 2-((1S,3aR,6aS)-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)octahydrocyclopenta[c]pyrrole-1-carboxamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000366] To a solution of 6-chloro-4-methoxy-1H-indole-2-carboxylic acid (363.64 mg, 1.61 mmol, 1.2 *eq*), methyl (2S)-2-[[(3S,3aS,6aR)-1,2,3,3a,4,5,6,6a-octahydrocyclopenta[c]pyrrole-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (472 mg, 1.34 mmol, 1 *eq*) in DCM (10 mL) was added DMAP (410.19 mg, 3.36 mmol, 2.5 *eq*), and then EDCI (514.93 mg, 2.69 mmol, 2 *eq*). The resulting mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was poured into H_2O 30 mL at 20 °C, and then extracted with DCM (35 mL * 3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 80/1 to 30/1) to give methyl (2S)-2-[[(3S,3aS,6aR)-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (650 mg, 1.16 mmol, 86.57% yield) as a yellow solid.

Step 9: (1S,3aR,6aS)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)octahydrocyclopenta[c]pyrrole-1-carboxamide

[000367] A solution of methyl (2S)-2-[[(3S,3aS,6aR)-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (650 mg, 1.16 mmol, 1 *eq*) in NH_3/MEOH (7 M, 13.00 mL, 78.27 *eq*) was stirred at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (3S,3aS,6aR)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carboxamide (630 mg, crude) as a yellow solid.

Step 10: (1S,3aR,6aS)-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)octahydrocyclopenta[c]pyrrole-1-carboxamide

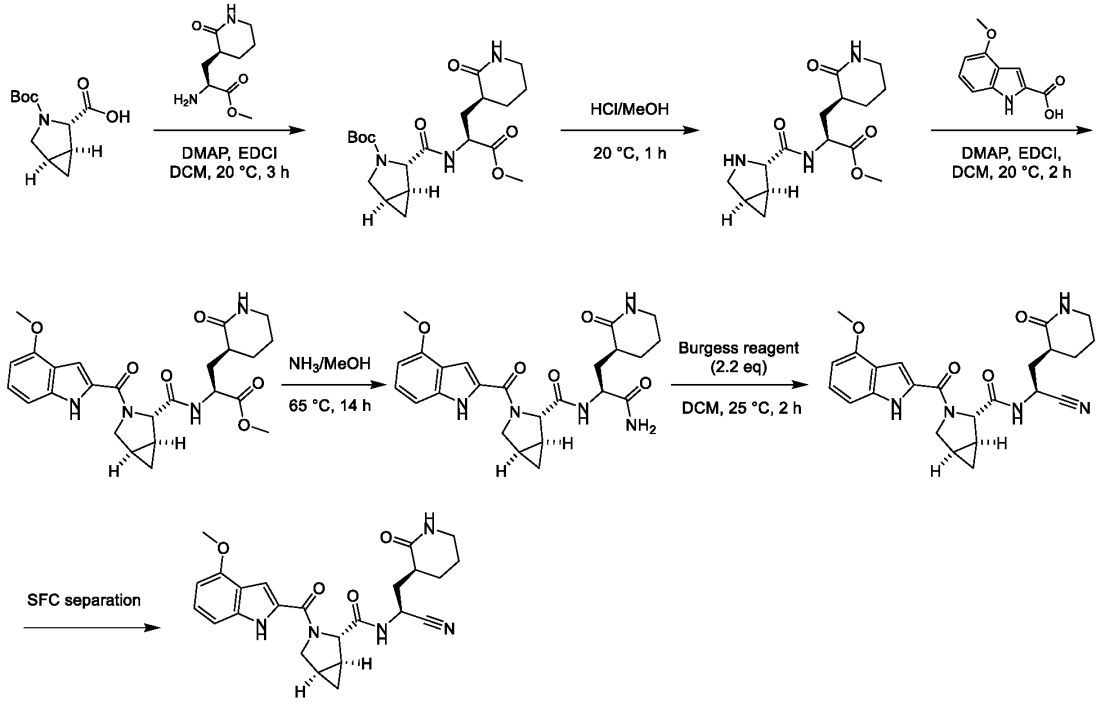
[000368] To a solution of (3S,3aS,6aR)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carboxamide (630 mg, 1.16 mmol, 1 *eq*) in DCM (12 mL) was added Burgess reagent (551.91 mg, 2.32 mmol, 2 *eq*). The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was poured into H_2O 30 mL at 20 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250*50mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 45%-75%,10min) to give (3S,3aS,6aR)-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carboxamide (215 mg, 408.73 umol, 35.30% yield, 100% purity) as a white solid.

[000369] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.69 (s, 1H), 8.92 (d, J = 7.9 Hz, 1H), 7.83 (s, 1H), 7.18 - 6.85 (m, 2H), 6.57 (s, 1H), 4.95 (d, J = 7.1 Hz, 1H), 4.74 - 4.30 (m, 1H), 4.16 (d, J = 8.9 Hz, 1H), 3.97 - 3.62 (m, 4H), 3.33 - 3.26 (m, 1H), 2.95 - 2.75 (m, 1H), 2.69 - 2.57 (m, 1H), 2.23 - 1.32 (m, 10H), 1.24 - 0.68 (m, 6H)

[000370] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80k) δ = 11.37 (s, 1H), 8.85 - 8.58 (m, 1H), 7.51 (s, 1H), 7.10 (s, 1H), 6.88 (s, 1H), 6.55 (s, 1H), 5.01 - 4.88 (m, 1H), 4.49 (s, 1H), 4.08 (s, 1H), 3.92 (s, 3H), 3.74 (d, J = 4.5, 10.8 Hz, 1H), 3.00 (s, 4H), 2.88 - 2.75

(m, 1H), 2.65 - 2.54 (m, 2H), 2.22 - 2.10 (m, 1H), 2.08 - 1.92 (m, 2H), 1.90 - 1.71 (m, 3H), 1.68 - 1.58 (m, 2H), 1.57 - 1.47 (m, 2H), 1.19 (s, 3H), 1.08 (s, 3H).

Example 298. Synthesis of viral protease inhibitor compound 1219



Step 1: (1S,2S,5R)-tert-butyl 2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

[000371] To a solution of (1S,2S,5R)-3-tert-butoxycarbonyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (500 mg, 2.20 mmol, 1 *eq*), methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl] propanoate (755.22 mg, 2.64 mmol, 70% purity, 1.2 *eq*) in DCM (15 mL) was added DMAP (537.58 mg, 4.40 mmol, 2 *eq*) and EDCI (632.66 mg, 3.30 mmol, 1.5 *eq*). The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was quenched by addition H_2O (40 mL), and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (SiO_2, Methanol:Dichloromethane = 10:1) to give tert-butyl (1S,2S,5R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-

piperidyl]methyl]ethyl]carbamoyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (811 mg, 1.47 mmol, 66.61% yield, 74% purity) as a white solid. MS (ESI) *m/z* 410.2 $[M+H]^+$.

Step 2: (S)-methyl 2-((1S,2S,5R)-3-azabicyclo[3.1.0]hexane-2-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000372] A solution of tert-butyl (1S, 2S, 5R)-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl] methyl] ethyl] carbamoyl]-3-azabicyclo [3.1.0] hexane-3-carboxylate (750 mg, 1.83 mmol, 1 *eq*) in HCl/MeOH (4M, 14 mL) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove HCl/MeOH, and DCM (20 mL) was added and was concentrated under reduced pressure (repeat three times) to give methyl (2S)-2-[[(1S, 2S, 5R)-3-azabicyclo [3.1.0] hexane-2-carbonyl] amino]-3-[(3S)-2-oxo-3-piperidyl] propanoate (500 mg, crude, HCl) as a white solid. MS (ESI) *m/z* 310.2 $[M+H]^+$.

Step 3: (S)-methyl 2-((1S,2S,5R)-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000373] To a solution of methyl (2S)-2-[[(1S,2S,5R)-3-azabicyclo[3.1.0]hexane-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (800 mg, 2.59 mmol, 1 *eq*), 4-methoxy-1H-indole-2-carboxylic acid (494.40 mg, 2.59 mmol, 1 *eq*) in DCM (20 mL) was added DMAP (631.86 mg, 5.17 mmol, 2 *eq*) and EDCI (743.60 mg, 3.88 mmol, 1.5 *eq*). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Ethyl acetate/MeOH = 5/1) to give methyl (2S)-2-[[(1S, 2S, 5R)-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo [3.1.0] hexane-2-carbonyl] amino]-3-[(3S)-2-oxo-3-piperidyl] propanoate (810 mg, 1.59 mmol, 61.67% yield, 95% purity) as a white solid. MS (ESI) *m/z* 483.2 $[M+H]^+$.

Step 4: (1S,2S,5R)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide

[000374] A solution of methyl (2S)-2-[[(1S,2S,5R)-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.1.0]hexane-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (810 mg, 1.76 mmol, 1 *eq*) in NH_3MeOH (7 M, 10 mL, 39.74 *eq*) was stirred at 65 °C

for 14 h. Upon completion, the reaction mixture was concentrated under reduced pressure to remove HN_3/MeOH, and DCM (30 mL) was added and was concentrated under reduced pressure (repeat three times) to give (1S,2S,5R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide (800 mg, crude) as a white solid. MS (ESI) *m/z* 468.2 $[M+H]^+$.

Step 5: (1S,2S,5R)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide

[000375] To a solution of (1S,2S,5R)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide (810 mg, 1.73 mmol, 1 *eq*) in DCM (10 mL) was added burgess reagent (908.33 mg, 3.81 mmol, 2.2 *eq*). The mixture was stirred at 25 °C for 2 h. Upon completion, the DCM was removed under N_2. The residue was purified by prep-TLC (SiO_2, EA:MeOH = 20:1) to give desired compound (460 mg, purity 98%) as a white solid, which was further separated by SFC (column: REGIS(S,S)WHELK-O1(250 mm * 25 mm,10 um); mobile phase: [Neu-ETOH]; B%: 50%-50%, 7 min) to give (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide Isomer 1 (120 mg, 266.96 umol, 15.41% yield, 100% purity) as a white solid. MS (ESI) *m/z* 450.2 $[M+H]^+$.

[000376] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.55 (s, 1H), 9.43 - 8.98 (m, 1H), 7.60 - 7.46 (m, 1H), 7.11 (q, *J* = 8.3 Hz, 1H), 7.06 - 6.97 (m, 1H), 6.96 - 6.59 (m, 1H), 6.55 - 6.43 (m, 1H), 5.07 (q, *J* = 7.7 Hz, 1H), 4.92 - 4.63 (m, 1H), 4.18 - 3.95 (m, 2H), 3.93 - 3.78 (m, 3H), 3.14 - 2.86 (m, 2H), 2.32 - 2.14 (m, 2H), 1.83 - 1.36 (m, 6H), 1.30 - 1.01 (m, 1H), 0.89 - 0.75 (m, 1H), 0.21 (br d, *J* = 3.8 Hz, 1H).

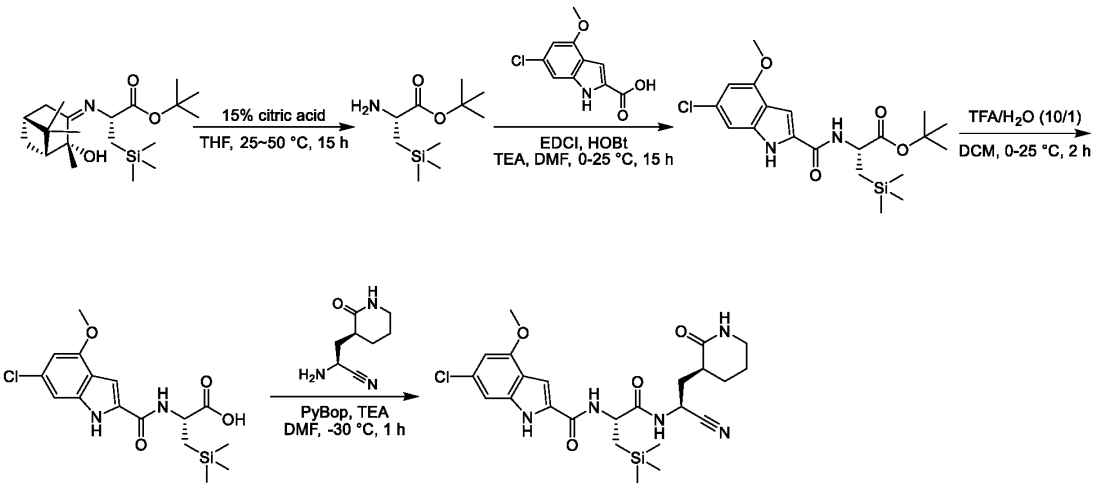
[000377] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ = 11.29 (br s, 1H), 9.10 - 8.56 (m, 1H), 7.27 (br d, *J* = 1.3 Hz, 1H), 7.16 - 6.74 (m, 3H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.11 - 5.00 (m, 1H), 4.83 - 4.72 (m, 1H), 4.06 (br d, *J* = 9.9 Hz, 2H), 3.90 (s, 3H), 3.18 - 3.08 (m, 2H), 2.31 - 2.21 (m, 2H), 1.92 - 1.40 (m, 7H), 0.88 - 0.78 (m, 1H), 0.21 (q, *J* = 4.1 Hz, 1H).

[000378] To give (1S,2S,5R)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-(4-methoxy-1H-indole-2-carbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide Isomer 2 (182 mg, 392.75 umol, 22.67% yield, 97% purity) as a white solid. MS (ESI) *m/z* 450.2 $[M+H]^+$.

[000379] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.61 - 11.48 (m, 1H), 9.26 - 8.95 (m, 1H), 7.58 - 7.43 (m, 1H), 7.17 - 6.97 (m, 2H), 6.96 - 6.56 (m, 1H), 6.55 - 6.46 (m, 1H), 5.12 - 5.03 (m, 1H), 4.82 - 4.66 (m, 1H), 4.16 - 4.00 (m, 2H), 3.92 - 3.82 (m, 3H), 3.13 - 2.96 (m, 2H), 2.33 (br s, 2H), 1.88 - 1.38 (m, 7H), 0.86 - 0.74 (m, 1H), 0.25 - 0.11 (m, 1H).

[000380] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ = 11.37 - 11.24 (m, 1H), 8.99 - 8.67 (m, 1H), 7.30 - 7.22 (m, 1H), 7.15 - 7.09 (m, 1H), 7.07 - 7.02 (m, 1H), 6.96 - 6.80 (m, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.13 - 5.00 (m, 1H), 4.79 - 4.71 (m, 1H), 4.13 - 3.94 (m, 2H), 3.90 (s, 3H), 3.18 - 3.09 (m, 2H), 2.31 - 2.08 (m, 2H), 1.94 - 1.57 (m, 6H), 1.50 - 1.38 (m, 1H), 0.87 - 0.77 (m, 1H), 0.24 - 0.15 (m, 1H).

Example 299. Synthesis of viral protease inhibitor compound 1221



Step 1: (R)-tert-butyl 2-amino-3-(trimethylsilyl)propanoate

[000381] To a solution of tert-butyl (2R)-2-[(Z)-[(2R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-ylidene]amino]-3-trimethylsilyl-propanoate (1.2 g, 3.26 mmol, 1 *eq*) in THF (6 mL) was added a solution of citric acid (18 mL, 15% purity). The mixture was stirred at 50 °C for 3 h. LCMS showed the reaction was not completed, then was

stirred for 12 h further. Upon completion, THF was removed in vacuum, the aqueous layer was extracted with EtOAc (15 mL*2) in order to remove the chiral inductor. Then the pH was increased to 8 - 9 with potassium carbonate. The free amine was then extracted with EtOAc (3 * 30 mL). The organic layer was combined, dried over Na_2SO_4 concentrated at room temperature due to the amine volatility to give tert-butyl (2R)-2-amino-3-trimethylsilyl-propanoate (510 mg, 2.35 mmol, 71.87% yield) as light yellow oil. MS (ESI) *m/z* 218.1$[M+H]^+$

Step 2: (R)-tert-butyl 2-(6-chloro-4-methoxy-1H-indole-2-carboxamido)-3-(trimethylsilyl)propanoate

[000382] To a solution of 6-chloro-4-methoxy-1H-indole-2-carboxylic acid (477.45 mg, 2.12 mmol, 1 *eq*) in DMF (5 mL) was added tert-butyl (2R)-2-amino-3-trimethylsilyl-propanoate (460 mg, 2.12 mmol, 1 *eq*), EDCI (527.36 mg, 2.75 mmol, 1.3 *eq*), TEA (642.38 mg, 6.35 mmol, 883.61 uL, 3 *eq*), and HOBt (371.72 mg, 2.75 mmol, 1.3 *eq*) was added at 0 °C. The resulting reaction was stirred at 25 °C for 1 h. LCMS showed the reaction was not completed, then EDCI (527.36 mg, 2.75 mmol, 1.3 *eq*), HOBt (371.72 mg, 2.75 mmol, 1.3 *eq*) and TEA (363.50 mg, 3.59 mmol, 0.5 mL, 1.70 *eq*) was added and was stirred for 14 h further. Upon completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with EA (20 mL * 2). The combined organic layers were washed with brine (10 mL*5), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (SiO_2 PE/EA = 10:1) to give tert-butyl (2R)-2-[(6-chloro-4-methoxy-1H-indole-2-carbonyl) amino]-3-trimethylsilyl-propanoate (770 mg, 1.79 mmol, 84.76% yield, 99% purity) as a light yellow solid. MS (ESI) *m/z* 369.1$[M+H-56]^+$

Step 3: (R)-2-(6-chloro-4-methoxy-1H-indole-2-carboxamido)-3-(trimethylsilyl)propanoic acid

[000383] To a solution of tert-butyl (2R)-2-[(6-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoate (750 mg, 1.76 mmol, 1 *eq*) in DCM (9 mL) was added TFA/H_2O 10:1 (6 mL) at 0 °C. Then the reaction was stirred at 25 °C for 2 h. Upon completion, the reaction was concentrated in vacuum to dryness (below 30 °C).The residue was poured into water (20 mL). The aqueous phase was extracted

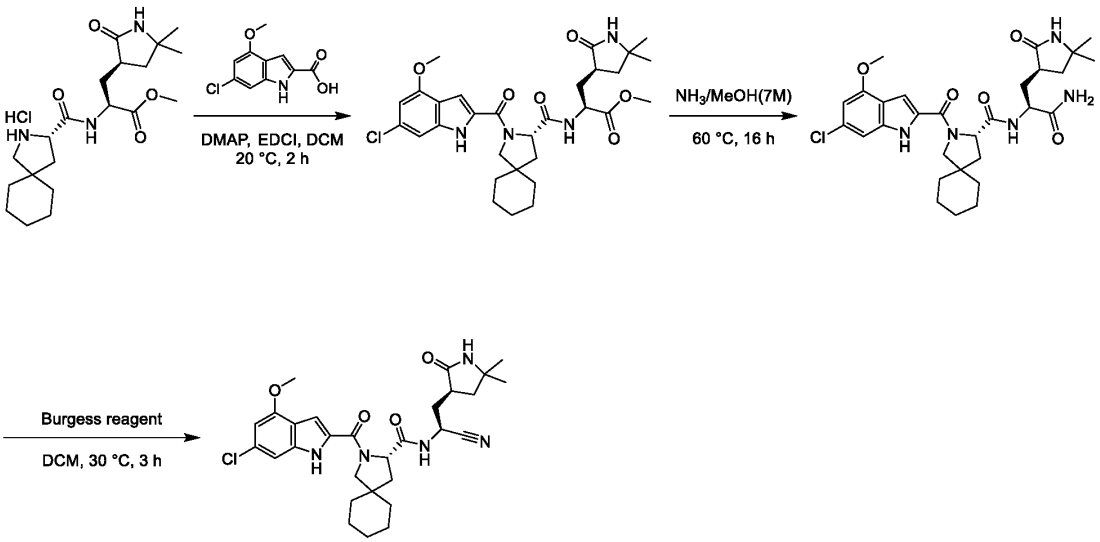
with ethyl acetate (12 mL*2). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give (2R)-2-[(6-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoic acid (740 mg, crude) as a light yellow solid. MS (ESI) *m/z* 369.1$[M+H]^+$

Step 4: 6-chloro-N-((R)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-1-oxo-3-(trimethylsilyl)propan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000384] To a solution of (2R)-2-[(6-chloro-4-methoxy-1H-indole-2-carbonyl)amino]-3-trimethylsilyl-propanoic acid (100 mg, 271.09 umol, 1 *eq*) and (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanenitrile (67.99 mg, 406.63 umol, 1.5 *eq*) in DMF (2 mL) was added a solution of PyBOP (211.61 mg, 406.63 umol, 1.5 *eq*) and TEA (82.29 mg, 813.26 umol, 113.20 uL, 3 *eq*) in DMF (2 mL) at -30 °C. Then the reaction was stirred at -30 °C for 1 h. Upon completion, the reaction mixture was quenched with water (10 mL) at -30 °C, then was extrated with EA (10 mL * 2), the combined organic phase was dried over Na_2SO_4, and concentrated. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 40%-70%, 8 min to give the product. The residue was purified by SFC column: DAICEL CHIRALPAK AD (250 mm * 30mm, 10 um); mobile phase: [0.1% NH_3H_2O IPA]; B%: 40% - 40%, 12 min to give Isomer 1 (Rt=1.344 min) 6-chloro-N-[(1R)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-2-oxo-1-(trimethylsilylmethyl)ethyl]-4-methoxy-1H-indole-2-carboxamide (4.39 mg, 8.40 umol, 3.10% yield, 99.1% purity) as a white solid. MS (ESI) *m/z* 518.1 $[M+H]^+$

[000385] 1H NMR (400MHz, MeOD-d_4) δ = 7.21 (s, 1H), 7.05 (s, 1H), 6.52 (d, J=1.4 Hz, 1H), 5.08 (br dd, J=6.1, 9.8 Hz, 1H), 4.59 (t, J=7.9 Hz, 1H), 3.93 (s, 3H), 3.23 - 3.16 (m, 2H), 2.53 - 2.36 (m, 2H), 2.03 - 1.84 (m, 2H), 1.78 (dt, J=4.6, 9.0 Hz, 1H), 1.72 - 1.60 (m, 1H), 1.55 - 1.43 (m, 1H), 1.20 (d, J=7.9 Hz, 2H), 0.10 (s, 9H)

Example 300. Synthesis of viral protease inhibitor compound 1227



Step 1: methyl (2S)-2-[[2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[000386] To a solution of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (0.1 g, 240.41 umol, 1 eq, HCl) and 6-chloro-4-methoxy-1H-indole-2-carboxylic acid (81.37 mg, 360.62 umol, 1.5 eq) in DCM (2 mL) was added DMAP (88.11 mg, 721.23 umol, 3 eq), EDCI (92.17 mg, 480.82 umol, 2 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O (10 mL) and extracted with DCM (5 mL * 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give methyl (2S)-2-[[2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (0.089 g, 128.85 umol, 53.60% yield, 85% purity) as yellow oil. MS (ESI) *m/z* 587.2 $[M+H]^+$

Step2: N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000387] The methyl (2S)-2-[[2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (0.079 g, 134.56 umol, 1 eq) in NH_3/MeOH (3 mL) was stirred at 60 °C

for 16 h. Upon completion, the reaction mixture was concentrated under pressure reduced to get the crude product N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (75 mg, crude) as yellow solid. MS (ESI) *m/z* 572.2 $[M+H]^+$

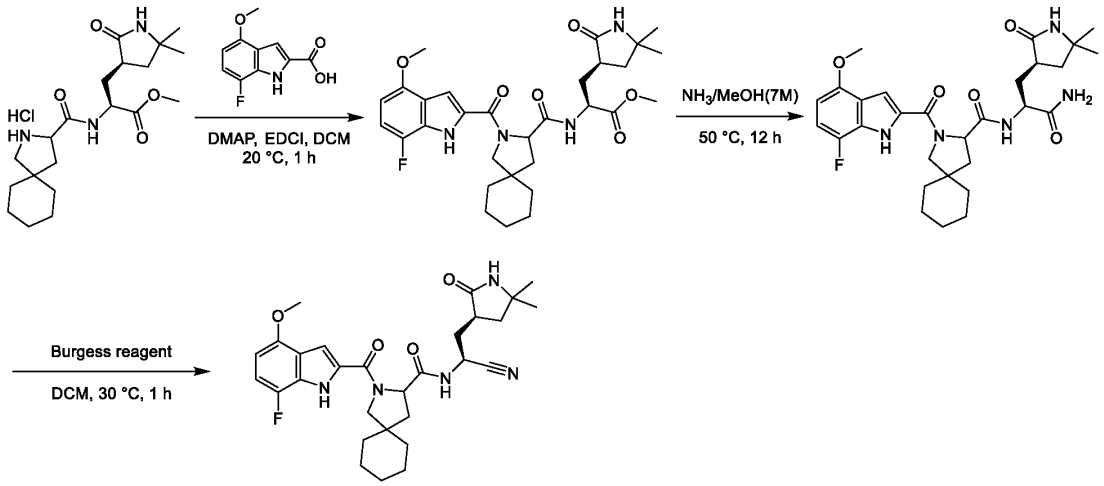
Step3: (3S)-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[000388] To a solution of N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (0.075 g, 131.10 umol, 1 eq) in DCM (1 mL) was added burgess reagent (93.73 mg, 393.29 umol, 3 eq). The mixture was stirred at 30 °C for 3 h. Upon completion, the mixture were quenched with water (0.5 mL) and blow-dried with N_2, and was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 40%-70%,8min) to give the product (3S)-2-(6-chloro-4-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (19 mg, 34.29 umol, 26.16% yield, 100% purity) as white solid. MS (ESI) *m/z* 554.2 $[M+H]^+$.

[000389] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.76 - 11.58 (m, 1H), 8.90 (d, *J* = 7.9 Hz, 1H), 7.81 (s, 1H), 7.15 - 6.85 (m, 2H), 6.57 (s, 1H), 4.92 (br d, *J* = 6.6 Hz, 1H), 4.49 (t, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.84 (br s, 1H), 3.67 (br d, *J* = 10.4 Hz, 1H), 2.66 - 2.58 (m, 1H), 2.28 - 2.04 (m, 2H), 1.99 (dd, *J* = 8.3, 11.8 Hz, 1H), 1.82 - 1.68 (m, 1H), 1.61 - 1.31 (m, 12H), 1.19 - 1.06 (m, 3H), 1.06 - 0.80 (m, 3H).

[000390] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ= 11.51 - 11.34 (m, 1H), 8.85 - 8.58 (m, 1H), 7.62 - 7.53 (m, 1H), 7.13 - 6.82 (m, 2H), 6.60 - 6.50 (m, 1H), 5.04 - 4.81 (m, 1H), 4.73 - 4.42 (m, 1H), 3.96 - 3.90 (m, 3H), 3.88 - 3.83 (m, 1H), 3.76 - 3.51 (m, 1H), 2.65 - 2.55 (m, 1H), 2.27 - 2.01 (m, 2H), 1.82 - 1.36 (m, 14H), 1.20 - 1.14 (m, 3H), 1.12 - 1.00 (m, 3H).

Example 301. Synthesis of viral protease inhibitor compound 1229



Step1: methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[2-(7-fluoro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]propanoate

[000391] To a solution of methyl (2S)-2-(2-azaspiro[4.5]decane-3-carbonylamino)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (82.86 mg, 199.20 umol, 1 eq, HCl), 7-fluoro-4-methoxy-1H-indole-2-carboxylic acid (0.05 g, 239.04 umol, 1.2 eq) in DCM (1 mL) was added DMAP (73.01 mg, 597.59 umol, 3 eq) and EDCI (76.37 mg, 398.39 umol, 2 eq). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (15 mL) and extracted with DCM (5 mL * 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure and was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give product methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[2-(7-fluoro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]propanoate (0.08 g, 141.27 umol, 57.11% yield, 97% purity) as white solid. MS (ESI) *m/z* 571.3 $[M+H]^+$

Step2: N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(7-fluoro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000392] A solution of methyl (2S)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]-2-[[2-(7-fluoro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]propanoate (0.07 g, 122.67 umol, 1 eq) in NH_3/MeOH (7M, 3 mL) was stirred at 50 °C for 12 h. Upon completion, the reaction mixture was concentrated under pressure reduced to get the crude product N-[(1S)-2-amino-1-[[(3R)-5,5-

dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(7-fluoro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (0.065 g, crude) as white solid. MS (ESI) *m/z* 556.3 $[M+H]^+$

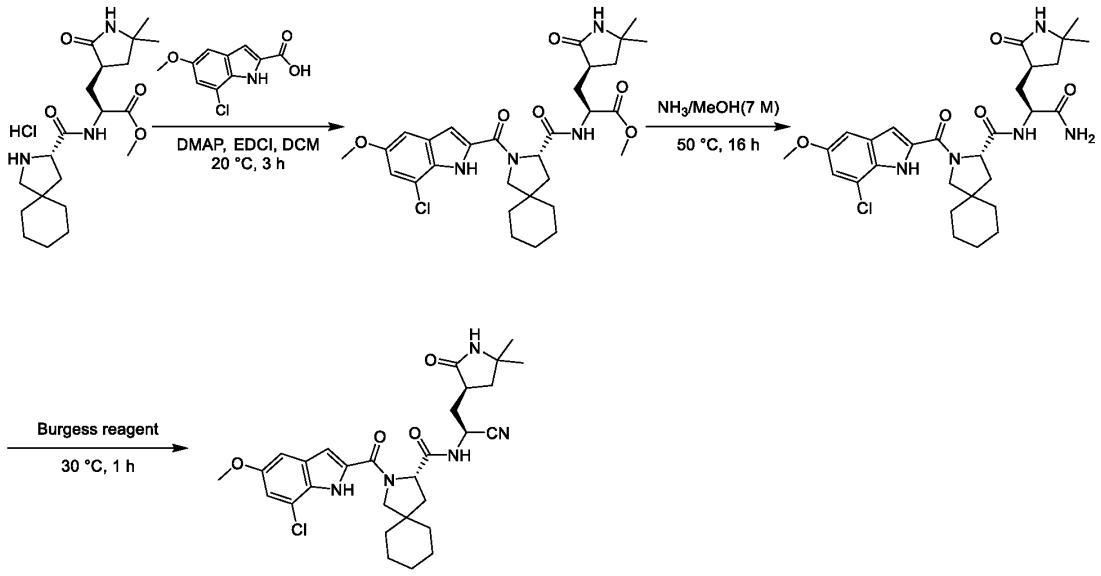
Step3: N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-(7-fluoro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000393] To a solution of N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(7-fluoro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (0.06 g, 102.58 umol, 95% purity, 1 eq) in DCM (1 mL) was added burgess reagent (97.79 mg, 410.34 umol, 4 eq), and the resulting mixture was stirred at 30 °C for 1 h. Upon completion, the mixture were quenched with water (0.5 mL) and blow-dried with N_2, and purified by prep-HPLC (column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 30%-65%,10min) to give the product N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-(7-fluoro-4-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (0.015 g, 26.67 umol, 26.00% yield, 95.6% purity) as white solid. MS (ESI) *m/z* 538.3 $[M+H]^+$

[000394] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.13 - 11.88 (m, 1H), 9.12 - 8.84 (m, 1H), 7.88 - 7.69 (m, 1H), 7.07 - 6.63 (m, 2H), 6.48 - 6.31 (m, 1H), 4.99 - 4.83 (m, 1H), 4.50 (t, J = 8.7 Hz, 1H), 3.90 - 3.77 (m, 4H), 3.68 (d, J = 10.3 Hz, 1H), 2.73 - 2.59 (m, 1H), 2.27 - 2.12 (m, 2H), 2.06 - 1.96 (m, 1H), 1.82 - 1.69 (m, 1H), 1.62 - 1.29 (m, 12H), 1.19 - 1.06 (m, 3H), 1.05 - 0.87 (m, 3H).

[000395] ^{1}H NMR (400 MHz, DMSO-d_6, 273+80K) δ = 11.73 - 11.58 (m, 1H), 8.80 - 8.61 (m, 1H), 7.66 - 7.51 (m, 1H), 7.05 - 6.80 (m, 2H), 6.52 - 6.28 (m, 1H), 5.00 - 4.84 (m, 1H), 4.73 - 4.48 (m, 1H), 3.92 - 3.80 (m, 4H), 3.75 - 3.50 (m, 1H), 2.65 - 2.54 (m, 1H), 2.29 - 2.18 (m, 1H), 2.11 - 1.93 (m, 1H), 1.87 - 1.61 (m, 2H), 1.58 - 1.28 (m, 12H), 1.20 - 1.14 (m, 3H), 1.10 - 1.00 (m, 3H).

Example 302. Synthesis of viral protease inhibitor compound 1231



Step 1: methyl (2S)-2-[[(3S)-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[000396] To a mixture of methyl (2S)-2-[[(3S)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (600 mg, 1.44 mmol, 1 *eq*, HCl) in DCM (10 mL) was added 7-chloro-5-methoxy-1H-indole-2-carboxylic acid (650.92 mg, 2.88 mmol, 2 *eq*), DMAP (440.56 mg, 3.61 mmol, 2.5 *eq*) and EDCI (553.05 mg, 2.88 mmol, 2 *eq*). The mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Petroleum ether:Ethyl acetate = 5/1 to 0/1) to get product methyl (2S)-2-[[(3S)-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (620 mg, 844.82 umol, 58.57% yield, 80% purity) as yellow solid. MS (ESI) *m/z* 587.3 $[M+H]^+$.

Step 2: (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide

[000397] A mixture of methyl (2S)-2-[[(3S)-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-

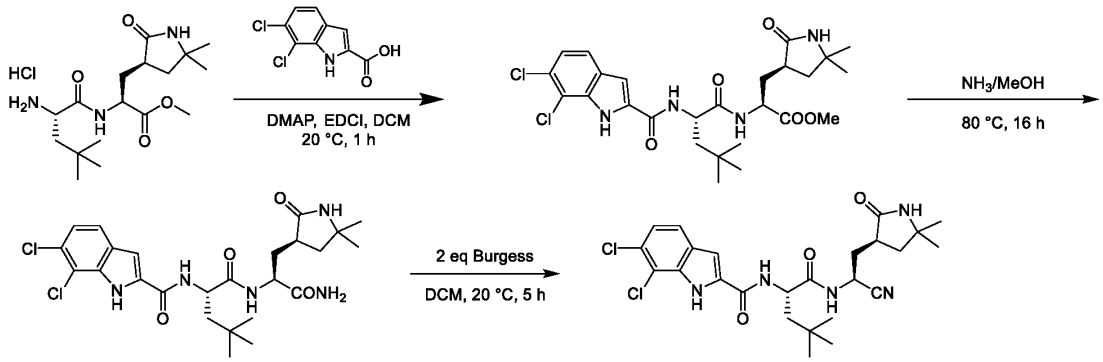
pyrrolidin-3-yl]propanoate (620 mg, 844.82 umol, 80% purity, 1 *eq*) in NH_3/MeOH (7 M, 10 mL, 82.86 *eq*) was stirred at 50 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to get the product (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (480 mg, crude) as yellow solid. MS (ESI) *m/z* 572.3 $[M+H]^+$.

Step 3: (3S)-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[000398] To a mixture of (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-2-azaspiro[4.5]decane-3-carboxamide (480 mg, 839.02 umol, 1 *eq*) in DCM (6 mL) was added burgess reagent (599.83 mg, 2.52 mmol, 3 *eq*). The mixture was stirred at 30 °C for 1 h. Upon completion, the mixture were quenched with water (1 mL) and blow-dried with N_2. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 35% - 70%, 8 min) to get the product (3S)-2-(7-chloro-5-methoxy-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-azaspiro[4.5]decane-3-carboxamide (215.9 mg, 386.54 umol, 46.07% yield, 99.2% purity) as white solid. MS (ESI) *m/z* 554.3 $[M+H]^+$.

[000399] ^1H NMR (400 MHz, DMSO-d_6) δ = 11.51 - 11.25 (m, 1H), 9.03 - 8.86 (m, 1H), 7.87 - 7.73 (m, 1H), 7.17 - 7.10 (m, 1H), 7.03 (s, 1H), 7.00 - 6.96 (m, 1H), 4.97 - 4.76 (m, 1H), 4.49 (t, *J* = 8.6 Hz, 1H), 3.70 - 3.86 (m, 4H), 3.63 (d, *J* = 10.4 Hz, 1H), 2.78 - 2.63 (m, 1H), 2.30 - 2.11 (m, 2H), 2.04 - 1.95 (m, 1H), 1.85 - 1.68 (m, 1H), 1.64 - 1.28 (m, 12H), 1.18 - 1.08 (m, 3H), 1.05 - 0.86 (m, 3H).

Example 303. Synthesis of viral protease inhibitor compound 1237



Step 1: (S)-methyl2-((S)-2-(6,7-dichloro-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000400] To a solution of 6,7-dichloro-1H-indole-2-carboxylic acid (91.31 mg, 396.92 umol, 1 eq) and methyl (2*S*)-2-[[(2*S*)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (150 mg, 396.92 umol, 1 eq, HCl) in DCM (5 mL) was added DMAP (96.98 mg, 793.85 umol, 2 eq) and EDCI (152.18 mg, 793.85 umol, 2 eq). The mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O (30 mL), and then extracted with EA (20 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, PE:EA = 0:1) to give the product methyl(2*S*)-2-[[(2*S*)-2-[(6,7-dichloro-1*H*-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (110 mg, 198.74 umol, 50.07% yield) as a yellow solid. MS (ESI) *m/z* 553.2 $[M+H]^+$

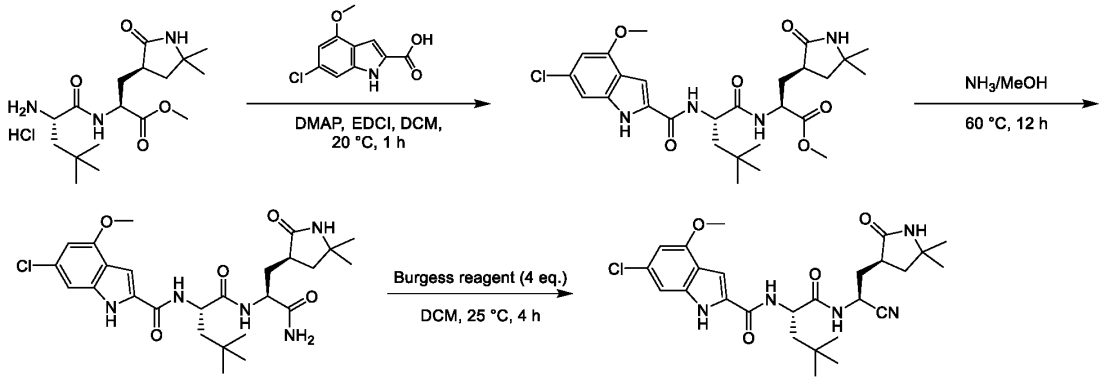
Step 2: N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-6,7-dichloro-1H-indole-2-carboxamide

[000401] A mixture of methyl (2*S*)-2-[[(2*S*)-2-[(6,7-dichloro-1*H*-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (110 mg, 198.74 umol, 1 eq) in NH_3/MeOH (7 M, 7.86 mL, 276.74 eq) was stirred at 80 °C for 16 h. Upon completion, the mixture was concentrated under the reduced pressure to give the product *N*-[(1*S*)-1-[[(1*S*)-2-amino-1-[[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-3,3-dimethyl-butyl]-6,7-dichloro-1*H*-indole-2-carboxamide (100 mg, crude) as a yellow solid. MS (ESI) *m/z* 538.2 $[M+H]^+$

Step 3: 6,7-dichloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-1H-indole-2-carboxamide

[000402] To a solution of *N*-[(1*S*)-1-[[(1*S*)-2-amino-1-[[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-3,3-dimethyl-butyl]-6,7-dichloro-1*H*-indole-2-carboxamide (90 mg, 167.14 umol, 1 eq) in DCM (3 mL) was added burgess reagent (79.66 mg, 334.28 umol, 2 eq). The mixture was stirred at 20 °C for 5 h. Upon completion, the mixture was concentrated under the reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 40% - 70%, 8 min) to give the product 6,7-dichloro-*N*-[(1*S*)-1-[[(1*S*)-1-cyano-2-[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]carbamoyl]-3,3- dimethyl-butyl]-1*H*-indole-2-carboxamide (20 mg, 38.24 umol, 22.88% yield, 99.5% purity) as a white solid. MS (ESI) *m/z* 520.2 $[M+H]^+$ ^1H NMR (400 MHz, MeOD-d_4) δ = 7.56 (d, *J* = 8.4 Hz, 1H), 7.27 - 7.15 (m, 2H), 5.00 (dd, *J* = 5.6, 10.4 Hz, 1H), 4.65 (dd, *J* = 4.6, 8.2 Hz, 1H), 2.78 (dd, *J* = 5.6, 8.2 Hz, 1H), 2.36 - 2.07 (m, 1H), 2.10 (dd, *J* = 8.6, 12.4 Hz, 1H), 1.95 - 1.84 (m, 2H), 1.83 - 1.74 (m, 1H), 1.65 - 1.52 (m, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 1.05 - 1.01 (m, 9H).

Example 304. Synthesis of viral protease inhibitor compound 1239



Step 1: (S)-methyl2-((S)-2-(6-chloro-4-methoxy-1H-indole-2-carboxamido)-4,4-dimethylpentanamido)-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanoate

[000403] To a solution of methyl(2*S*)-2-[[(2*S*)-2-amino-4,4-dimethyl-pentanoyl]amino]-3-[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (200 mg, 529.23 umol, 1 eq, HCl) and 6-chloro-4-methoxy-1*H*-indole-2-carboxylic acid (143.29 mg, 635.08umol,

1.2 eq) in DCM (10 mL) was added EDCI (202.91 mg, 1.06 mmol, 2 eq) and DMAP (193.97 mg, 1.59 mmol, 3 eq), the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was diluted with H_2O (60 mL) and extracted with DCM (40 mL * 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give the product methyl(2*S*)-2-[[(2*S*)-2-[(6-chloro-4-methoxy-1*H*-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (180 mg, 327.83 umol, 61.95% yield) as a white solid. MS (ESI) *m/z* 549.3 $[M+H]^+$.

Step2:N-((S)-1-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-6-chloro-4-methoxy-1H-indole-2-carboxamide

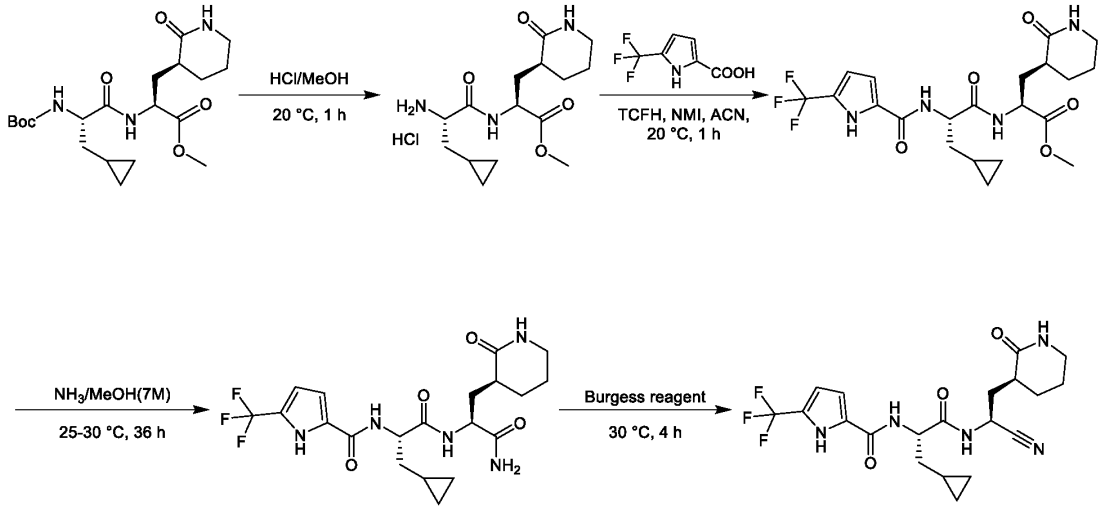
[000404] A solution of methyl(2*S*)-2-[[(2*S*)-2-[(6-chloro-4-methoxy-1*H*-indole-2-carbonyl)amino]-4,4-dimethyl-pentanoyl]amino]-3-[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (180.00 mg, 327.83 umol, 1 eq) in NH_3/MeOH (7 M, 5 mL, 106.76 eq) was stirred at 60 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the product *N*-[(1*S*)-1-[[(1*S*)-2-amino-1-[[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-3,3-dimethyl-butyl]-6-chloro-4-methoxy-1*H*-indole-2-carboxamide (150 mg, crude) as a yellow solid. MS (ESI) *m/z* 534.3 $[M+H]^+$.

Step3:6-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-4-methoxy-1H-indole-2-carboxamide

[000405] To a solution of *N*-[(1*S*)-1-[[(1*S*)-2-amino-1-[[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-3,3-dimethyl-butyl]-6-chloro-4-methoxy-1*H*-indole-2-carboxamide (130.00 mg, 243.42 umol, 1 eq) in DCM (6 mL) was added Burgess reagent (232.04 mg, 973.70 umol, 4 eq), the mixture was stirred at 25 °C for 4 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 35% - 65%, 8 min) to give the product 6-chloro-*N*-[(1*S*)-1-[[(1*S*)-1-cyano-2-[(3*R*)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]carbamoyl]-3,3-

dimethyl- butyl]-4-methoxy-1*H*-indole-2-carboxamide (30 mg, 58.14 umol, 23.88% yield, 100% purity) as a white solid. MS (ESI) *m/z* 516.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD-d_4) δ = 7.23 (s, 1H), 7.04 (s, 1H), 6.52 (d, *J* = 1.4 Hz, 1H), 4.99 (dd, *J* = 5.8, 10.4 Hz, 1H), 4.63 (dd, *J* = 4.6, 8.3 Hz, 1H), 3.93 (s, 3H), 2.78 - 2.68 (m, 1H), 2.41 - 2.29 (m, 1H), 2.09 (dd, *J* = 8.6, 12.4 Hz, 1H), 1.92 - 1.75 (m, 3H), 1.62 - 1.54 (m, 1H), 1.21 (s, 3H), 1.13 - 0.96 (m, 12H)。

Example 305. Synthesis of viral protease inhibitor compound 1249



Step 1: (S)-methyl 2-((S)-2-amino-3-cyclopropylpropanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000406] A solution of (*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl) amino)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (5 g, 12.15 mmol, 1 *eq*) in HCl/MeOH (4 M, 60 mL) was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was concerntration in vacuum to obtained (*S*)-methyl 2-((*S*)-2-amino-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl) propanoate (4 g, crude) as a white solid. MS (ESI) *m/z* 312.2 $[M+H]^+$

Step 2: (S)-methyl2-((S)-3-cyclopropyl-2-(5-(trifluoromethyl)-1H-pyrrole-2-carboxamido)propanamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000407] To a solution of (*S*)-methyl 2-((*S*)-2-amino-3-cyclopropylpropanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (680 mg, 1.95 mmol, 1 *eq*, HCl) and 5-

(trifluoromethyl)-1*H*-pyrrole-2-carboxylic acid (350.12 mg, 1.95 mmol, 1 *eq*) in CH_3CN (8 mL) was added with NMI (481.50 mg, 5.86 mmol, 467.48 uL, 3 *eq*) and TCFH (548.52 mg, 1.95 mmol, 1 *eq*), the mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was diluted with water (20 mL), and then extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuum and was purified by column chromatography (SiO_2, PE/EA = 1/0 to 0/1) then re-purified by prep-TLC (SiO_2, EA:MeOH = 10:1) to obtained (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(5-(trifluoromethyl)-1*H*-pyrrole-2-carboxamido)propanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (350 mg, 740.81 umol, 37.89% yield) as a yellow solid. MS (ESI) *m/z* 473.2 $[M+H]^+$

Step 3: N-((S)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-(trifluoromethyl)-1H-pyrrole-2-carboxamide

[000408] A solution of (*S*)-methyl 2-((*S*)-3-cyclopropyl-2-(5-(trifluoromethyl)-1*H*-pyrrole-2-carboxamido)propanamido)-3-((*S*)-2-oxopiperidin-3-yl)propanoate (300 mg, 634.98 umol, 1 *eq*) in NH_3/MeOH (10 mL, 7M) was stirred at 25 °C for 12 h, then was stirred at 30 °C for 24 h. Upon the reaction completion, the mixture was concentrated in vacuum to obtained *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxamide (330 mg, crude) as a yellow solid. MS (ESI) *m/z* 458.2 $[M+H]^+$

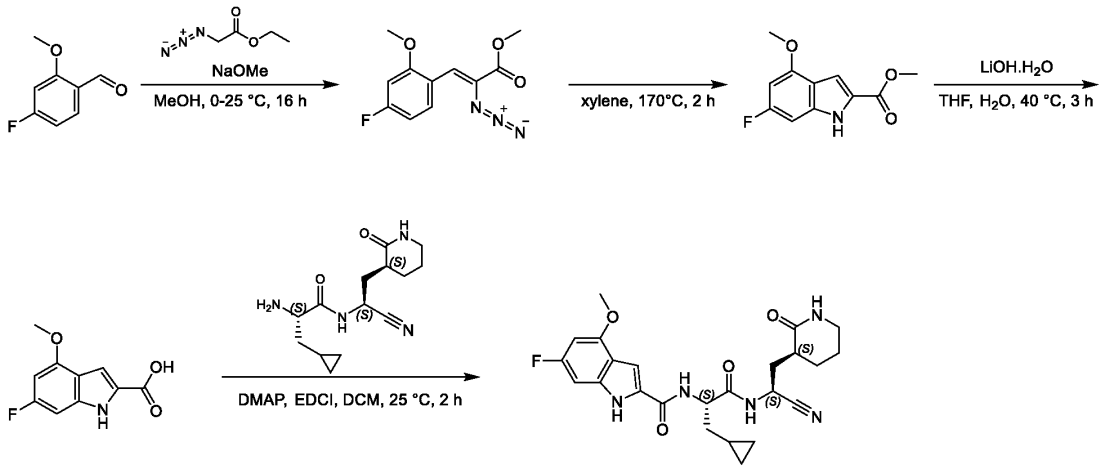
Step 4: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-5-(trifluoromethyl)-1H-pyrrole-2-carboxamide

[000409] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*S*)-2-oxopiperidin-3-yl)propan-2-yl)amino) -3-cyclopropyl-1-oxopropan-2-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxamide (300 mg, 459.07 umol, 1 *eq*) in DCM (5 mL) was added burgess reagent (328.20 mg, 1.38 mmol, 3 *eq*), and the mixture was stirred at 30 °C for 4 h. Upon the reaction completion, the mixture was quenched by water (1 mL) and was dried by blowing N_2 and was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40mm * 10um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 20%-50%, 8min) to obtained *N*-((*S*)-1-(((*S*)-1-cyano-2-((*S*)-2-

oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1- oxopropan-2-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxamide (4.36 mg, 9.92 umol, 2.16% yield, 100% purity) as a white solid. MS (ESI) *m/z* 440.1 $[M+H]^+$

[000410] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.73 (s, 1H), 8.96 - 8.85 (m, 1H), 8.45 - 8.32 (m, 1H), 7.52 (s, 1H), 6.95 (d, J = 3.2 Hz, 1H), 6.66 - 6.57 (m, 1H), 5.05 (q, J = 8.0 Hz, 1H), 4.48 - 4.39 (m, 1H), 3.13 - 3.03 (m, 2H), 2.29 - 2.18 (m, 2H), 1.88 - 1.65 (m, 4H), 1.62 - 1.50 (m, 1H), 1.49 - 1.34 (m, 2H), 0.83 - 0.71 (m, 1H), 0.47 - 0.35 (m, 2H), 0.22 - 0.04 (m, 2H).

Example 306. Synthesis of viral protease inhibitor compound 1251



Step 1: (Z)-methyl 2-azido-3-(4-fluoro-2-methoxyphenyl)acrylate

[000411] A solution of NaOMe (700.98 mg, 12.98 mmol, 2 *eq*) was added 4-fluoro-2-methoxy-benzaldehyde (1 g, 6.49 mmol, 1 *eq*), ethyl 2-azidoacetate (1.68 g, 12.98 mmol, 1.48 mL, 2 *eq*) in MeOH (30mL) at -10 °C was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was quenched by addition H_2O 30 mL, and then extracted with EA (30 mL * 3). The combined organic layers were washed with brine 30 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 to 50/1) to give methyl (Z)-2-azido-3-(4-fluoro-2-methoxy-phenyl) prop-2-enoate (685 mg, 2.45 mmol, 37.83% yield, 90% purity) as a yellow solid.

Step 2: methyl 6-fluoro-4-methoxy-1H-indole-2-carboxylate

[000412] A solution of methyl (Z)-2-azido-3-(4-fluoro-2-methoxy-phenyl)prop-2-enoate (685 mg, 2.73 mmol, 1 *eq*) in xylene (10 mL) was stirred at 170 °C for 2 h. Upon completion, the reaction mixture was cooled to 25 °C, and then get solid through filtration and washed with PE 10 mL to give methyl 6-fluoro-4-methoxy-1H-indole-2-carboxylate (400 mg, crude) as a white solid. MS (ESI) *m/z* 224.1 $[M+H]^+$.

Step 3: 6-fluoro-4-methoxy-1H-indole-2-carboxylic acid

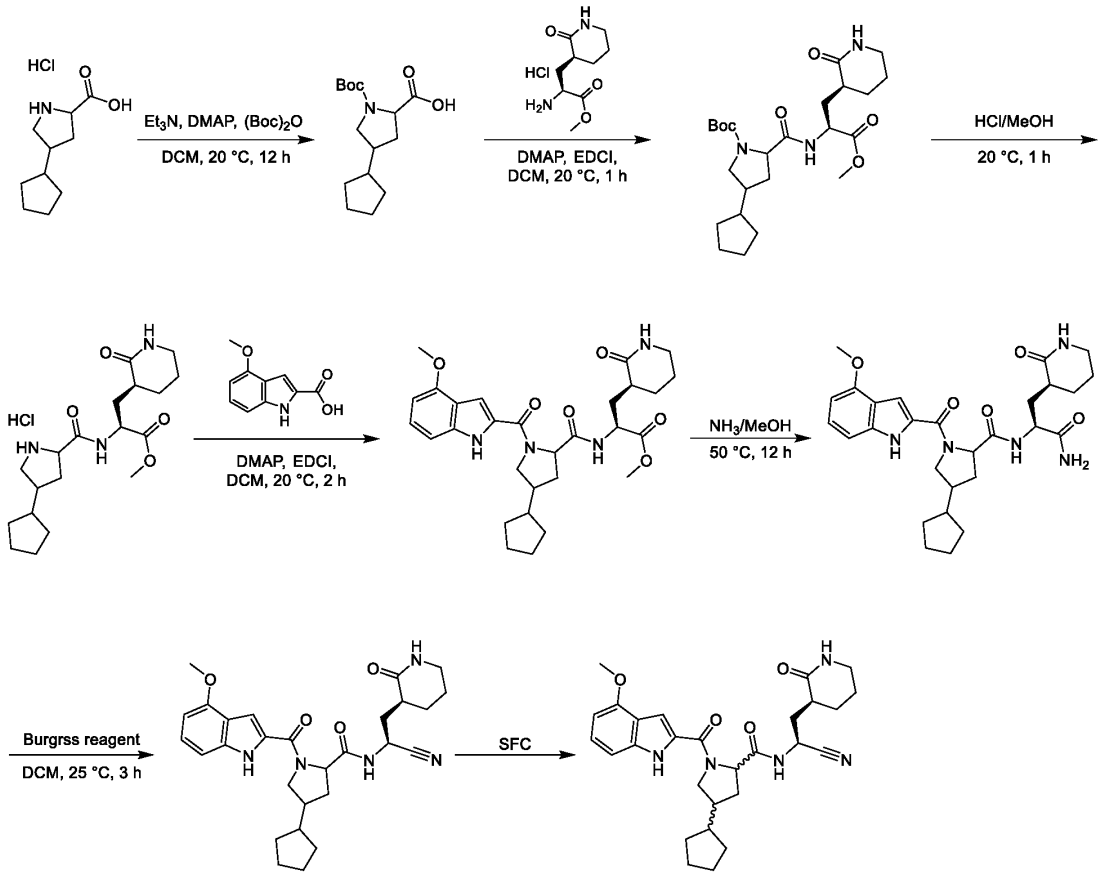
[000413] A solution of methyl 6-fluoro-4-methoxy-1H-indole-2-carboxylate (400 mg, 1.79 mmol, 1 *eq*) in THF (8 mL) and H_2O (2 mL) was added $LiOH.H_2O$ (150.41 mg, 3.58 mmol, 2 *eq*). The mixture was stirred at 40 °C for 3 h. Upon completion, the reaction mixture was quenched by addition H_2O 20 mL, the aqueous phase was added HCl (1M) to pH = 3 and extracted with DCM (15 mL * 3). The combined organic layers were washed with brine 20 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-fluoro-4-methoxy-1H-indole-2-carboxylic acid (460 mg, crude) as a white solid. MS (ESI) *m/z* 210.0 $[M+H]^+$.

Step 4: N-((S)-1-(((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-6-fluoro-4-methoxy-1H-indole-2-carboxamide

[000414] A solution of 6-fluoro-4-methoxy-1H-indole-2-carboxylic acid (81.01 mg, 387.28 umol, 1.1 *eq*), (2S)-2-amino-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-3-cyclopropyl-propanamide (140 mg, 352.08 umol, 70% purity, 1 *eq*) in DCM (4 mL) was added DMAP (86.02 mg, 704.15 umol, 2 *eq*) and EDCI (101.24 mg, 528.11 umol, 1.5 *eq*). The mixture was stirred 25 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 15 mL, and then extracted with EA (15 mL * 3). The combined organic layers were washed with brine 20 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 25%-55%, 8 min) to give N-[(1S)-2-[[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-6-fluoro-4-methoxy-1H-indole-2-carboxamide (20 mg, 41.75 umol, 11.86% yield, 98% purity) as a white solid. MS (ESI) *m/z* 470.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.64 (s, 1H), 8.89 (d, *J* = 8.2 Hz, 1H),

8.49 (d, J = 7.5 Hz, 1H), 7.52 (br s, 1H), 7.36 (d, J = 1.5 Hz, 1H), 6.73 (dd, J = 1.3, 9.5 Hz, 1H), 6.46 (dd, J = 2.0, 12.1 Hz, 1H), 5.10 - 5.01 (m, 1H), 4.48 - 4.40 (m, 1H), 3.90 (s, 3H), 3.15 - 3.03 (m, 2H), 2.29 - 2.22 (m, 2H), 1.87 - 1.68 (m, 4H), 1.61 - 1.35 (m, 3H), 0.85 - 0.73 (m, 1H), 0.48 - 0.34 (m, 2H), 0.25 - 0.04 (m, 2H)

Example 307. Synthesis of viral protease inhibitor compound 1253



Step 1: 1-(tert-butoxycarbonyl)-4-cyclopentylpyrrolidine-2-carboxylic acid

[000415] To a solution of 4-cyclopentylpyrrolidine-2-carboxylic acid (900 mg, 4.10 mmol, 1 eq, HCl) in DCM (20 mL) was added TEA (497.41 mg, 4.92 mmol, 684.19 uL, 1.2 eq), DMAP (100.09 mg, 819.27 umol, 0.2 eq) and $(Boc)_2O$ (983.42 mg, 4.51 mmol, 1.04 mL, 1.1 eq), and then the resulting mixtrue was stirred at 20 °C for 12 h. Upon completion, the reaction mixture was quenched by addition H_2O 50 mL at 0 °C, and then extracted with DCM 30 mL. The aqueous layers was added 1M HCl to pH = 4, then extracted with DCM (30 mL * 3), washed with brine 40 mL, dried over

Na_2SO_4, filtered and concentrated under reduced pressure to give the 1-tert-butoxycarbonyl-4-cyclopentyl-pyrrolidine-2-carboxylic acid (750 mg, crude) as a yellow solid.

Step 2: tert-butyl 4-cyclopentyl-2-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate

[000416] To a solution of 1-tert-butoxycarbonyl-4-cyclopentyl-pyrrolidine-2-carboxylic acid (750 mg, 2.65 mmol, 1 eq) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (904.92 mg, 3.44 mmol, 90% purity, 1.3 eq, HCl) in DCM (20 mL) was added DMAP (808.38 mg, 6.62 mmol, 2.5 eq) and EDCI (1.01 g, 5.29 mmol, 2 eq), and then the mixture was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H_2O 60 mL at 0 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine 40 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:0 to 0:1) to give the tert-butyl 4-cyclopentyl-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl] methyl] ethyl] carbamoyl] pyrrolidine-1-carboxylate (1.0 g, 2.15 mmol, 81.15% yield) as a white solid. MS (ESI) *m/z* 466.2 $[M+H]^+$

Step 3: (2S)-methyl 2-(4-cyclopentylpyrrolidine-2-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000417] A mixture of tert-butyl 4-cyclopentyl-2-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]pyrrolidine-1-carboxylate (1 g, 2.15 mmol, 1 eq) in HCl/MeOH (4 M, 20 mL, 37.25 eq) was stirred at 20 °C for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the methyl (2S)-2-[(4-cyclopentylpyrrolidine-2-carbonyl) amino]-3-[(3S)-2-oxo-3-piperidyl] propanoate (0.8 g, crude, HCl) as a white solid.

Step 4: (2S)-methyl 2-(4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000418] To a solution of methyl (2S)-2-[(4-cyclopentylpyrrolidine-2-carbonyl)amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.8 g, 1.99 mmol, 1 eq, HCl) and 4-methoxy-1H-indole-2-carboxylic acid (456.64 mg, 2.39 mmol, 1.2 eq) in DCM (20 mL) was added DMAP (607.91 mg, 4.98 mmol, 2.5 eq) and EDCI (763.13 mg, 3.98 mmol, 2 eq), and

then the resulting mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by addition H_2O 60 mL at 0 °C, and then extracted with DCM (30 mL * 3). The combined organic layers were washed with brine 40 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:Ethyl acetate = 1:4 to 0:1) to give the methyl (2S)-2-[[4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (0.9 g, 1.60 mmol, 80.59% yield, 96% purity) as a yellow solid. MS (ESI) *m/z* 539.3 $[M+H]^+$

Step 5: N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[000419] A mixture of methyl (2S)-2-[[4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl) pyrrolidine-2-carbonyl] amino]-3-[(3S)-2-oxo-3-piperidyl] propanoate (0.9 g, 1.67 mmol, 1 eq) in NH_3/MeOH (4 M, 20 mL, 47.88 eq), the mixture was stirred at 50 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give the N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl] methyl] ethyl]-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl) pyrrolidine-2-carboxamide (0.9 g, crude) as a white solid. MS (ESI) *m/z* 524.3 $[M+H]^+$

Step 6: N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide

[000420] To a solution of N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide (850 mg, 1.62 mmol, 1 *eq*) in DCM (8 mL) was added burgess reagent (773.68 mg, 3.25 mmol, 2 *eq*), then the mixture was stirred at 25 °C for 1 h. LCMS showed ~50% reactant 1 remained, then burgess reagent (386.84 mg, 1.62 mmol, 1.00 *eq*) was added and stirred for 2 h additional. Upon completion, the reaction was quenched with water (0.8 mL), stirred for 10 min and concentrated in vacuum (bellow 30 °C). The residue was purified by prep-HPLC(column: Waters Xbridge BEH C18 250 * 50 mm * 10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B%: 35%-75%,10 min) then was purified by SFC column: DAICEL CHIRALCEL OD(250 mm * 30 mm, 10 um); mobile phase: [Neu-MeOH]; B%: 45%-45%, 15 min to give Isomer 1 (Rt = 1.409 min), N-[(1S)-1-cyano-2-[(3S)-2-oxo-

3-piperidyl]ethyl]-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide Isomer 1 (75.72 mg, 149.76 umol, 9.23% yield, 100% purity) as white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$

[000421] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.21 (br s, 1H), 8.64 (br s, 1H), 7.23 - 7.04 (m, 3H), 6.89 (br s, 1H), 6.53 (d, *J* =7.3 Hz, 1H), 4.98 (br d, *J* =7.2 Hz, 1H), 4.58 (br s, 1H), 4.12 (dd, *J* =7.8, 10.0 Hz, 1H), 3.91 (s, 3H), 3.50 (br s, 1H), 3.10 (br s, 2H), 2.47 - 2.06 (m, 5H), 1.90 - 1.74 (m, 4H), 1.71 - 1.46 (m, 7H), 1.45 - 1.13 (m, 3H)

[000422] To give N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl] ethyl]-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl) pyrrolidine-2-carboxamide Isomer 2 (98.03 mg, 193.89 umol, 11.94% yield, 100% purity) as a white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$

[000423] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.20 (br s, 1H), 8.53 (br s, 1H), 7.09 (br dd, *J* =7.8, 16.0 Hz, 3H), 6.91 (br s, 1H), 6.61 - 6.43 (m, 1H), 4.97 (br s, 1H), 4.57 (br s, 1H), 4.12 (br d, *J* =8.8 Hz, 1H), 3.91 (br d, *J* =7.7 Hz, 3H), 3.53 (br s, 1H), 3.09 (br s, 2H), 2.28 - 2.02 (m, 4H), 1.90 - 1.54 (m, 12H), 1.45 - 1.11 (m, 3H)

[000424] To give N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide Isomer 3 (250 mg, 494.46 umol, 23.04% yield, 100% purity) as a white solid. The product was re-purified by SFC (column: DAICEL CHIRALPAK AS (250 mm * 30 mm, 10 um); mobile phase: [Neu-EtOH]; B%: 50%-50%, 15 min) to give N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl)pyrrolidine-2-carboxamide Isomer 3_1 (90.63 mg, 179.25 umol, 11.04% yield, 100% purity) as a white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$

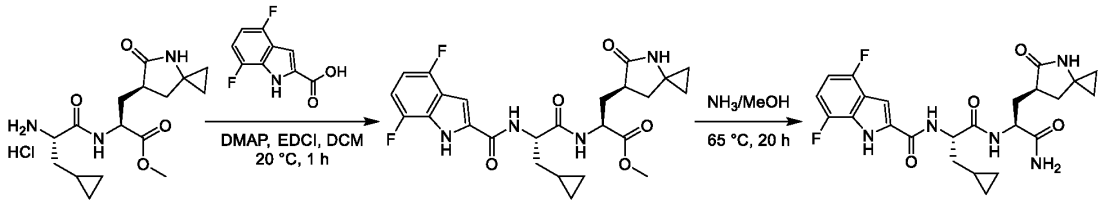
[000425] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.25 (br s, 1H), 8.62 (br s, 1H), 7.19 - 7.04 (m, 3H), 6.88 (br s, 1H), 6.52 (d, *J* =7.3 Hz, 1H), 5.00 (br d, *J* =6.4 Hz, 1H), 4.68 (br s, 1H), 4.07 (br s, 1H), 3.91 (s, 3H), 3.52 (br s, 1H), 3.10 (br s, 2H), 2.36 - 2.13 (m, 3H), 2.05 - 1.68 (m, 8H), 1.67 - 1.37 (m, 6H), 1.20 (br d, *J* =10.6 Hz, 2H)

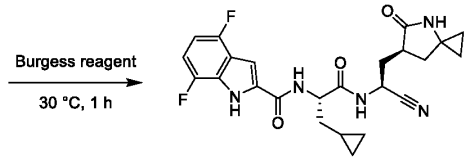
[000426] To give N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl] ethyl]-4-cyclopentyl-1-(4-methoxy-1H-indole-2-carbonyl) pyrrolidine-2-carboxamide Isomer 3_2 (89.82 mg,

177.65 umol, 10.94% yield, 100% purity) as a white solid. MS (ESI) *m/z* 506.2 $[M+H]^+$

[000427] ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.24 (br s, 1H), 8.66 (br s, 1H), 7.37 - 7.01 (m, 3H), 6.89 (br s, 1H), 6.53 (br d, *J* =6.7 Hz, 1H), 5.00 (br s, 1H), 4.69 (br s, 1H), 4.05 (br s, 1H), 3.90 (br d, *J* =4.5 Hz, 3H), 3.51 (br s, 1H), 3.11 (br s, 2H), 2.31 - 2.19 (m, 3H), 2.07 - 1.68 (m, 8H), 1.65 - 1.38 (m, 6H), 1.20 (br s, 2H).

Example 308. Synthesis of viral protease inhibitor compound 1268





Step 1: methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,7-difluoro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]propanoate

[000428] To a solution of methyl (2S)-2-[[(2S)-2-amino-3-cyclopropyl-propanoyl]amino]-3-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]propanoate (200 mg, 555.79 umol, 1 *eq*, HCl) in DCM (5 mL) was added 4,7-difluoro-1H-indole-2-carboxylic acid (164.35 mg, 833.69 umol, 1.5 *eq*), DMAP (169.75 mg, 1.39 mmol, 2.5 *eq*) and EDCI (213.09 mg, 1.11 mmol, 2 *eq*). The mixture was stirred at 25 °C for 1 h. Upon completion, the reaction mixture was acidic at pH of 4~5 with 1 M HCl (50 mL) and extracted with DCM (30 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Petroleum ether:Ethyl acetate = 5/1~0/1) to get product methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,7-difluoro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-

yl]propanoate (100 mg, 199.00 umol, 35.81% yield) as white solid. MS (ESI) *m/z* 503.2 $[M+H]^+$.

Step 2: N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,7-difluoro-1H-indole-2-carboxamide

[000429] To a solution of methyl (2S)-2-[[(2S)-3-cyclopropyl-2-[(4,7-difluoro-1H-indole-2-carbonyl)amino]propanoyl]amino]-3-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]propanoate (100 mg, 199.00 umol, 1 *eq*) was added NH_3/MeOH (7 M, 2 mL, 70.35 *eq*). The mixture was stirred at 65 °C for 20 h. Upon completion, the mixture was concentrated under reduced pressure to give a residue, then was dissolved with DCM (10 mL * 3) and concentrated under reduced pressure to get the product N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,7-difluoro-1H-indole-2-carboxamide (90 mg, crude) as white solid. MS (ESI) *m/z* 488.2 $[M+H]^+$.

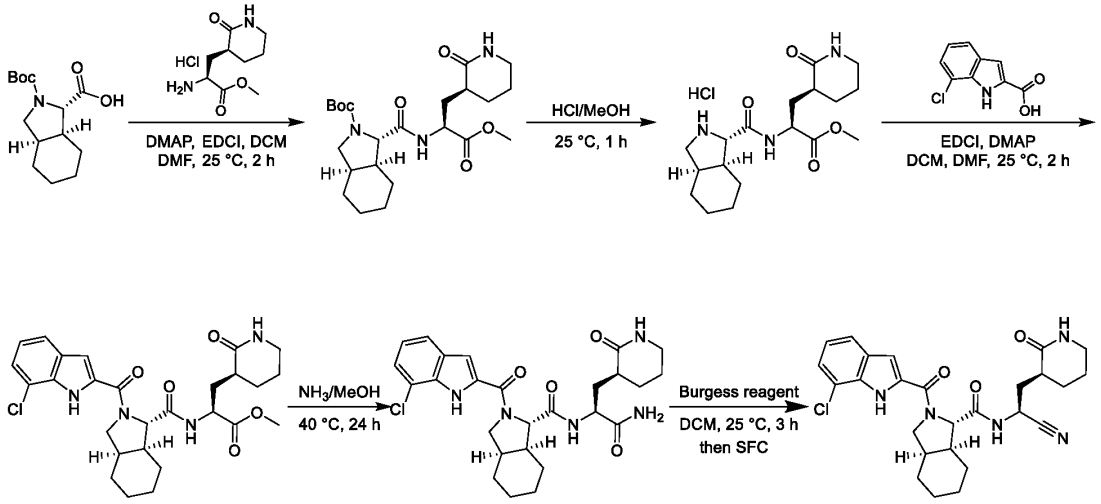
Step 3: N-[(1S)-2-[[(1S)-1-cyano-2-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,7-difluoro-1H-indole-2-carboxamide

[000430] To a solution of N-[(1S)-2-[[(1S)-2-amino-2-oxo-1-[[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]methyl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,7-difluoro-1H-indole-2-carboxamide (90 mg, 184.62 umol, 1 *eq*) in DCM (1 mL) was added burgess reagent (131.98 mg, 553.85 umol, 3 *eq*). The mixture was stirred at 30 °C for 1 h. Upon completion, the mixture were quenched with water (1 mL) and blow-dried with N_2. The residue was purified by prep-HPLC (column: Waters X bridge BEH C18 100 * 25 mm * 5 um; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 20% - 55%, 10 min) to get the product N-[(1S)-2-[[(1S)-1-cyano-2-[(6R)-5-oxo-4-azaspiro[2.4]heptan-6-yl]ethyl]amino]-1-(cyclopropylmethyl)-2-oxo-ethyl]-4,7-difluoro-1H-indole-2-carboxamide (10.52 mg, 21.96 umol, 11.89% yield, 98% purity) as white solid. MS (ESI) *m/z* 470.2 $[M+H]^+$.

[000431] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.45 (s, 1H), 8.98 (d, 1H), 8.70 (d, 1H), 7.80 (s, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.06 - 6.96 (m, 1H), 6.85 - 6.76 (m, 1H), 5.04 - 4.89 (m, 1H), 4.58 - 4.43 (m, 1H), 2.70 - 2.57 (m, 1H), 2.29 - 2.15 (m, 1H), 2.01 -

1.75 (m, 4H), 1.55 - 1.38 (m, 1H), 0.90 - 0.77 (m, 1H), 0.73 - 0.68 (m, 1H),0.62 - 0.48 (s, 3H), 0.47 - 0.38 (m, 2H), 0.26 - 0.01 (m, 2H).

Example 309. Synthesis of viral protease inhibitor compound 1282



Step 1: (1S,3aR,7aS)-tert-butyl 1-(((S)-1-methoxy-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)carbamoyl)hexahydro-1H-isoindole-2(3H)-carboxylate

[000432] A solution of (1S,3aR,7aS)-2-tert-butoxycarbonyl-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxylic acid (450 mg, 1.67 mmol, 1 *eq*) and methyl (2S)-2-amino-3-[(3S)-2-oxo-3-piperidyl]propanoate (571.23 mg, 2.17 mmol, 90% purity, 1.3 *eq*, HCl) in DMF (5 mL) and DCM (1.5 mL), were added EDCI (640.58 mg, 3.34 mmol, 2 *eq*) and DMAP (612.34 mg, 5.01 mmol, 3 *eq*), and then the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O 20 mL at 0 °C and then extracted with EA (10 mL * 2). The combined organic layers were washed with brine (10 mL*5), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (SiO_2 PE/EA = 1:1 to EA). Then diluted with EA (20 mL), and was washed with 15% citric acid(10 mL*2), the combined organic layers were washed with $NaHCO_3$(10 mL), brine(10 mL) dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl (1S,3aR,7aS)-1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-1,3,3a,4,5,6,7,7a-octahydroisoindole-2-

carboxylate (600 mg, 1.33 mmol, 79.53% yield) as a white solid. MS (ESI) *m/z* 452.3[M+H]$^+$

Step 2: (S)-methyl 2-((1S,3aR,7aS)-octahydro-1H-isoindole-1-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate hydrochloride

[000433] A solution of tert-butyl (1S,3aR,7aS)-1-[[(1S)-2-methoxy-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]carbamoyl]-1,3,3a,4,5,6,7,7a-octahydroisoindole-2-carboxylate (500 mg, 1.11 mmol, 1 *eq*) in HCl/MeOH (4 M, 10 mL, 36.12 *eq*) was stirre at 25 °C for 1 h. Upon completion, the reaction was concentrated in vacuum to give methyl (2S)-2-[[(1S,3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydro-1H-isoindole-1-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (430 mg, crude, HCl) as a white solid.

Step 3: (S)-methyl 2-((1S,3aR,7aS)-2-(7-chloro-1H-indole-2-carbonyl)octahydro-1H-isoindole-1-carboxamido)-3-((S)-2-oxopiperidin-3-yl)propanoate

[000434] To a solution of methyl (2S)-2-[[(1S,3aR,7aS)-2,3,3a,4,5,6,7,7a-octahydro-1H-isoindole-1-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (430 mg, 1.11 mmol, 1 *eq*, HCl) and 7-chloro-1H-indole-2-carboxylic acid (281.88 mg, 1.44 mmol, 1.3 *eq*) in DMF (6 mL) and DCM (2 mL), was added EDCI (425.01 mg, 2.22 mmol, 2 *eq*) and DMAP (406.29 mg, 3.33 mmol, 3 *eq*), then the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was diluted with H_2O (20 mL) at 0 °C and then extracted with EA (20 mL * 2). The combined organic layers were was washed with 15% citric acid (20 mL * 2), the combined organic layers were washed with $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (SiO_2 PE/EA = 0:1) to give methyl (2S)-2-[[(1S,3aR,7aS)-2-(7-chloro-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carbonyl]amino]-3-[(3S)-2-oxo-3-piperidyl]propanoate (440 mg, 798.45 umol, 72.03% yield, 96% purity) as a off-white solid. MS (ESI) *m/z* 529.2[M+H]$^+$

Step 4: (1S,3aR,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-2-(7-chloro-1H-indole-2-carbonyl)octahydro-1H-isoindole-1-carboxamide

[000435] A solution of methyl (2S)-2-[[(1S,3aR,7aS)-2-(7-chloro-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carbonyl]amino]-3-[(3S)-2-oxo-3-

piperidyl]propanoate (440 mg, 831.72 umol, 1 *eq*) in NH_3.MeOH (7 M, 12 mL, 101.00 *eq*) and the mixture was stirred at 40 °C fo 24 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give (1S,3aR,7aS)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide (430 mg, crude) as an off-white solid. MS (ESI) *m/z* 514.2 $[M+H]^+$

Step 5: (1S,3aR,7aS)-2-(7-chloro-1H-indole-2-carbonyl)-N-((S)-1-cyano-2-((S)-2-oxopiperidin-3-yl)ethyl)octahydro-1H-isoindole-1-carboxamide

[000436] To a solution of (1S,3aR,7aS)-N-[(1S)-2-amino-2-oxo-1-[[(3S)-2-oxo-3-piperidyl]methyl]ethyl]-2-(7-chloro-1H-indole-2-carbonyl)-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide (430 mg, 836.55 umol, 1 *eq*) in DCM (5 mL) was added Burgess reagent (598.08 mg, 2.51 mmol, 3 *eq*), and then the mixture was stirred at 25 °C for 3 h. Upon completion, the residue was quenched with water (0.5 mL) and was stirred for 10 min, then was concentrated bellow 30 °C. The residue was purified by prep-HPLC (HPLC column: Phenomenex Gemini-NX 80 * 40 mm * 3 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 25%-55%, 8 min. Then was purified by SFC to give Isomer 1 (Rt = 0.878 min) (1S,3aR,7aS)-2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide (103.07 mg, 207.80 umol, 24.84% yield, 100% purity) as a white solid. MS (ESI) *m/z* 496.1 $[M+H]^+$

[000437] ^{1}H NMR (400MHz, DMSO- d_6) (273+80K) δ = 11.13 (br s, 1H), 8.74 (br s, 1H), 7.62 (br s, 1H), 7.31 - 7.23 (m, 2H), 7.08 (br t, J=7.8 Hz, 2H), 5.00 (br s, 1H), 4.31 (br d, J=4.4 Hz, 1H), 4.08 - 3.88 (m, 1H), 3.73 (br d, J=7.1 Hz, 1H), 3.10 (br s, 2H), 2.41 (br s, 1H), 2.23 (br s, 3H), 1.84 (br s, 2H), 1.71 (br s, 2H), 1.59 - 1.33 (m, 9H)

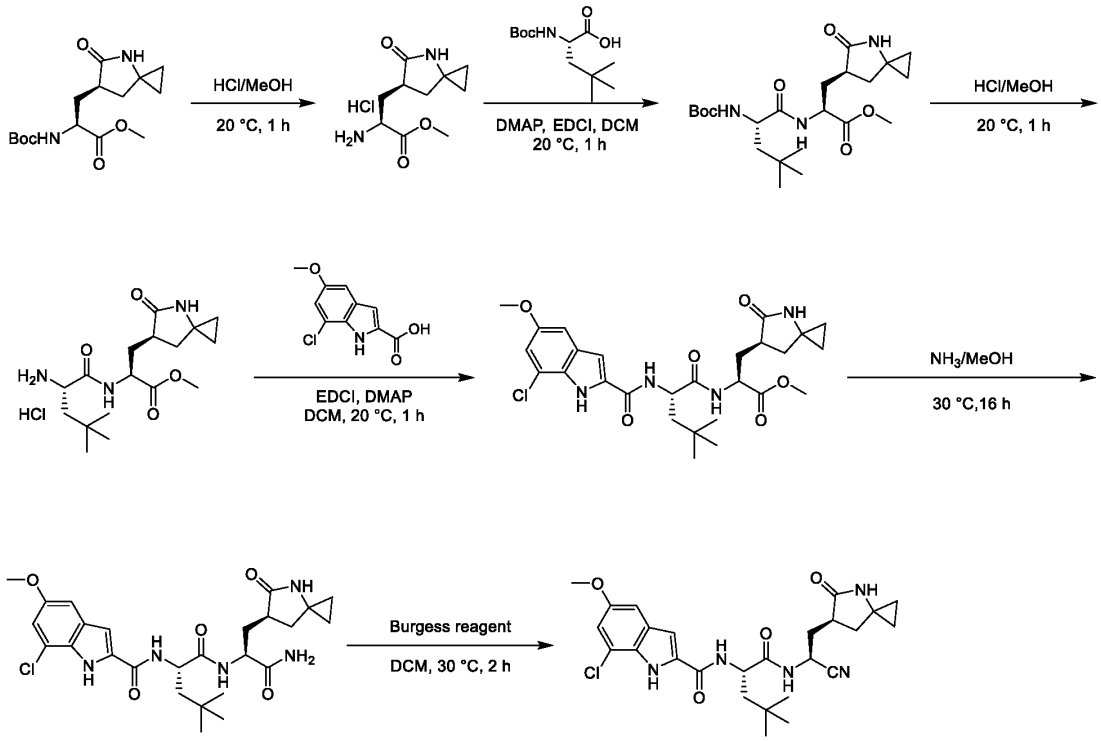
[000438] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.66 - 11.52 (m, 1H), 9.12 - 8.85 (m, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.32 - 7.25 (m, 1H), 7.16 (s, 1H), 7.11 - 7.01 (m, 1H), 5.11 - 4.94 (m, 1H), 4.42 - 4.19 (m, 1H), 3.98 (dd, *J* = 6.7, 10.0 Hz, 1H), 3.80 - 3.69 (m, 1H), 3.12 - 2.97 (m, 2H), 2.38 (br d, *J* = 4.5 Hz, 1H), 2.27 - 2.13 (m, 3H), 1.88 - 1.61 (m, 4H), 1.54 (br d, *J* = 4.8 Hz, 5H), 1.44 - 1.23 (m, 4H)

[000439] And Isomer 2 (Rt = 1.583 min) (1S,3aR,7aS)-2-(7-chloro-1H-indole-2-carbonyl)-N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-piperidyl]ethyl]-1,3,3a,4,5,6,7,7a-octahydroisoindole-1-carboxamide (99.03 mg, 199.66 umol, 23.87% yield, 100% purity) as a white solid. MS (ESI) *m/z* 496.1 $[M+H]^+$

[000440] ^{1}H NMR (400MHz, DMSO-d_6) (273+80K)δ = 11.11 (br s, 1H), 8.77 (br s, 1H), 7.60 (br s, 1H), 7.26 (br d, J=7.3 Hz, 2H), 7.17 - 6.98 (m, 2H), 5.00 (br s, 1H), 4.32 (br s, 1H), 3.93 (s, 1H), 3.69 (br s, 1H), 3.10 (br s, 2H), 2.44 - 2.18 (m, 4H), 1.80 (br s, 2H), 1.68 (br s, 2H), 1.54 (br s, 5H), 1.36 (br s, 4H)

[000441] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.59 (br s, 1H), 9.22 - 8.93 (m, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.58 - 7.46 (m, 1H), 7.34 - 7.24 (m, 1H), 7.16 (s, 1H), 7.11 - 6.99 (m, 1H), 5.13 - 4.90 (m, 1H), 4.46 - 4.24 (m, 1H), 3.98 (dd, *J* = 6.7, 10.0 Hz, 1H), 3.78 - 3.53 (m, 1H), 3.15 - 2.91 (m, 2H), 2.43 - 2.15 (m, 4H), 1.96 - 1.75 (m, 2H), 1.70 - 1.48 (m, 7H), 1.46 - 1.24 (m, 4H)

Example 310. Synthesis of viral protease inhibitor compound 1286



Step 1: (S)-methyl 2-amino-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate hydrochloride

[000442] A solution of (*S*)-methyl 2-((*tert*-butoxycarbonyl) amino)-3-((*R*)-5-oxo-4-azaspiro [2.4] heptan-6-yl) propanoate (250 mg, 800.36 umol, 1 *eq*) in HCl/MeOH (5 mL, 4M) was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was concerntration in vacuum to obtained (*S*)-methyl 2-amino-3-((*R*)-5-oxo-4-azaspiro [2.4] heptan-6-yl) propanoate hydrochloride (200 mg, crude, HCl) as a yellow solid.

Step 2: (S)-methyl2-((S)-2-((tert-butoxycarbonyl)amino)-4,4-dimethylpentanamido)-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate

[000443] To a solution of methyl (*S*)-methyl 2-amino-3-((*R*)-5-oxo-4-azaspiro [2.4]heptan-6-yl) propanoate hydrochloride (200 mg, 804.16 umol, 1 *eq*, HCl) and (2*S*)-2-(*tert*-butoxycarbonylamino)-4,4-dimethyl-pentanoic acid (217.00 mg, 884.58 umol, 1.1 *eq*) in DCM (10 mL) was added DMAP (196.49 mg, 1.61 mmol, 2 *eq*) and EDCI (308.32 mg, 1.61 mmol, 2 *eq*) at 20 °C, the mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was adjusted pH~1 with aq.HCl (15 mL, 1M), then was added addition of water (10 mL) and was extracted with DCM (9 mL * 3), then the organic phase was adjusted pH~7 with sat.$NaHCO_3$ (15 mL), then the organic phase was concerntration in vacuum and was purified by column (SiO_2, ninhydrin, PE:EA = 1:0 to 0:1) to obtained (2*S*)-2-[[(2*S*)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl] amino]-3-[(6*R*)-5- oxo-4-azaspiro[2.4]heptan-6-yl] propanoate (350 mg, 732.58 umol, 91.10% yield, 92% purity) as a white solid. MS (ESI) *m/z* 440.2 $[M+H]^+$

Step 3: (S)-methyl2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate

[000444] A solution of (2*S*)-2-[[(2*S*)-2-(tert-butoxycarbonylamino)-4,4-dimethyl-pentanoyl]amino]-3- [(6*R*)-5-oxo-4-azaspiro[2.4]heptan-6-yl] propanoate (160 mg, 364.01 umol, 1 *eq*) in HCl/MeOH (3 mL, 4 M) was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was concerntration in vacuum to obtained (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3- ((*R*)-5-oxo-4-azaspiro[2.4]heptan-6-yl) propanoate (100 mg, crude, HCl) as a white solid. MS (ESI) *m/z* 340.2 $[M+H]^+$

Step 4: (S)-methyl2-((S)-2-amino-4,4-dimethylpentanamido)-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate

[000445] To a solution of (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3-((*R*)-5-oxo-4-azaspiro[2.4] heptan-6-yl) propanoate (90 mg, 239.43 umol, 1 *eq*, HCl) and 7-chloro-5-methoxy-1*H*-indole-2-carboxylic acid (75.63 mg, 335.20 umol, 1.4 *eq*) in DCM (5 mL) was added DMAP (58.50 mg, 478.86 umol, 2 *eq*) and EDCI (91.80 mg, 478.86 umol, 2 *eq*), the mixture was stirred at 20 °C for 1 h. Upon the reaction completion, the mixture was added addtion water (15 mL) and was extracted with DCM (5 mL * 3), then was dried with Na_2SO_4, filtered and concerntration in vacuum and was purification by prep-TLC (SiO_2, EA = 1) to obtained (*S*)-methyl 2-((*S*)-2-amino-4,4-dimethylpentanamido)-3-((*R*)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propanoate (80 mg, 131.62 umol, 54.97% yield, 90% purity) as a white solid. MS (ESI) *m/z* 547.2 $[M+H]^+$

Step 5: N-((S)-1-(((S)-1-amino-1-oxo-3-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)propan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-5-methoxy-1H-indole-2-carboxamide

[000446] A solution of (*S*)-methyl 2-((*S*)-2-amino-4, 4-dimethylpentanamido)-3-((*R*)-5-oxo-4-azaspiro [2.4] heptan-6-yl) propanoate (70 mg, 127.96 umol, 1 *eq*) in NH_3/MeOH (4 mL, 7 M) was stirred at 30 °C for 16 h. Upon the reaction completion, the mixture was concerntration in vacuum to obtained *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*R*)-5-oxo-4-azaspiro [2.4] heptan-6-yl) propan-2-yl) amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-5-methoxy-1*H*-indole-2-carboxamide (70 mg, crude) as a white solid. MS (ESI) *m/z* 532.2 $[M+H]^+$

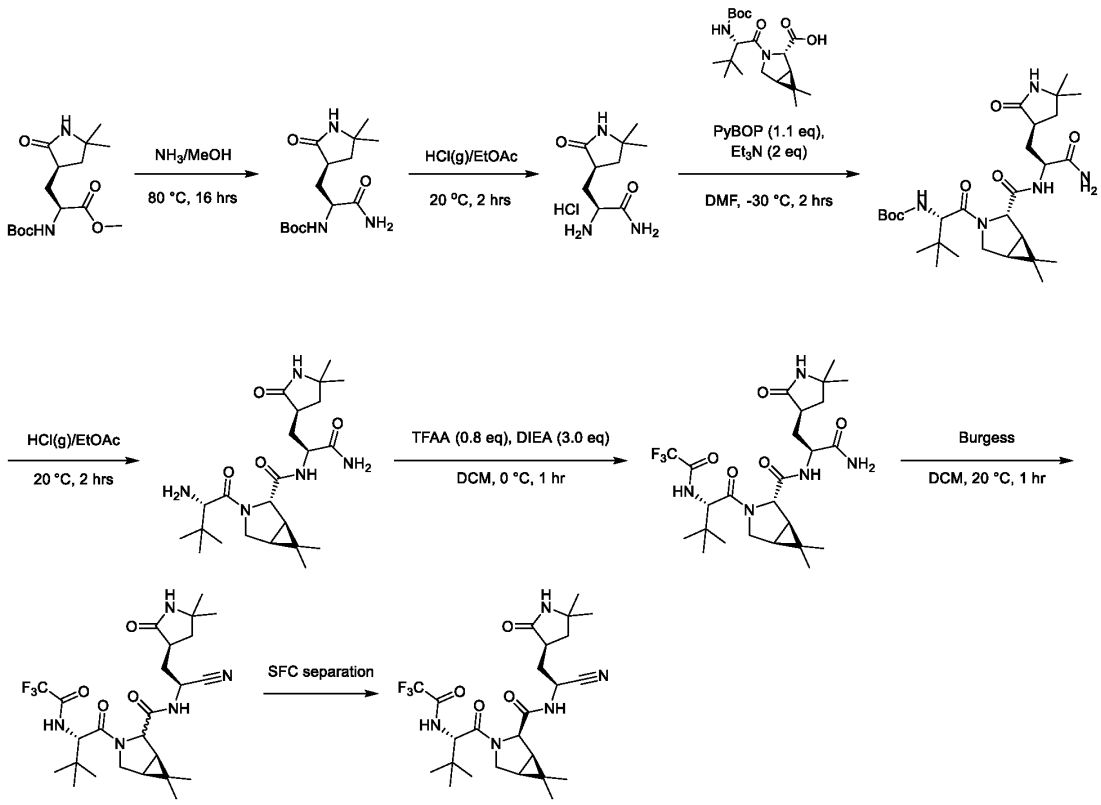
Step 6: 7-chloro-N-((S)-1-(((S)-1-cyano-2-((R)-5-oxo-4-azaspiro[2.4]heptan-6-yl)ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-5-methoxy-1H-indole-2-carboxamide

[000447] To a solution of *N*-((*S*)-1-(((*S*)-1-amino-1-oxo-3-((*R*)-5-oxo-4-azaspiro[2.4] heptan-6-yl) propan-2-yl) amino)-4,4-dimethyl-1-oxopentan-2-yl)-7-chloro-5-methoxy-1*H*-indole-2-carboxamide (60 mg, 112.78 umol, 1 *eq*) in DCM (2 mL) was added burgess reagent (80.62 mg, 338.33 umol, 3 *eq*), the mixture was stirred at 30 °C for 2 h. Upon the reaction completion, the mixture was quenched by water (0.5 mL) and was dried by blowing N_2 and was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5um; mobile phase: [water (10 mM NH_4HCO_3)-

ACN]; B%: 30%-60%, 10min) to obtained 7-chloro-*N*-((*S*)-1-(((*S*)-1-cyano-2-((*R*)-5-oxo-4-azaspiro[2.4]heptan-6-yl)ethyl)amino) -4,4-dimethyl-1-oxopentan-2-yl)-5-methoxy-1H-indole-2-carboxamide (15 mg, 28.89 umol, 25.62% yield, 99% purity) as a white solid. MS (ESI) *m/z* 514.1 $[M+H]^+$

[000448] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.55 (s, 1H), 9.02 (d, *J* = 8.0 Hz, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 7.82 - 7.73 (m, 1H), 7.18 - 7.11 (m, 2H), 7.00 (d, *J* = 2.2 Hz, 1H), 4.95 (q, *J* = 7.8 Hz, 1H), 4.61 - 4.53 (m, 1H), 3.78 (s, 3H), 2.64 - 2.58 (m, 1H), 2.24 - 2.15 (m, 1H), 1.99 - 1.91 (m, 2H), 1.90 - 1.81 (m, 1H), 1.77 - 1.65 (m, 2H), 0.94 (s, 9H), 0.75 - 0.67 (m, 1H), 0.57 - 0.43 (m, 3H).

Example 311. Synthesis of viral protease inhibitor compound 3075



Step 1: tert-butyl ((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)carbamate

[000449] A solution of methyl (2S)-2-(tert-butoxycarbonylamino)-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (10 g, 31.81 mmol, 1 *eq*) in NH_3/MeOH (80 mL)

was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. Then the mixture was dissolved in DCM (10 mL) and concentrated under reduced pressure for two times to give tert-butyl N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamate (8.9 g, crude) as light yellow gum and used directly next step.

Step 2: (S)-2-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)propanamide

[000450] A solution of tert-butyl N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamate (8.9 g, 29.73 mmol, 1 *eq*) in 4 M HCl/EtOAc (40 mL) was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. Then the mixture was dissolved in toluene (10 mL) and concentrated under reduced pressure for two times to give (2S)-2-amino-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanamide (5.13 g, crude, HCl) as white solid and used directly for next step.

Step 3: tert-butyl ((S)-1-((1R,2S,5S)-2-(((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)carbamoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate

[000451] To a solution of (1R,2S,5S)-3-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (0.5 g, 1.36 mmol, 1 *eq*) and (2S)-2-amino-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanamide (405.57 mg, 2.04 mmol, 1.5 *eq*) in DMF (5 mL) was added PyBOP (776.78 mg, 1.49 mmol, 1.1 *eq*) and cooled to -30 °C, the mixture was added Et_3N (274.62 mg, 2.71 mmol, 377.75 uL, 2 *eq*) at -30 °C. The mixture was stirred at -30 °C for 2 h. Upon completion, the reaction mixture was quenched by water (10 mL), and then extracted with ethyl acetate (6 mL * 2). The combined organic layers were washed with brine (10 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 20/1 to 0/1) to give tert-butyl N-[(1S)-1-[(1R,2S,5S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carbonyl]-2,2-dimethyl-propyl]carbamate (0.5 g, 909.59 umol, 67.03% yield) as a white solid. MS (ESI) *m/z* 436.2 $[M+H]^+$

Step 4: (1R,2S,5S)-3-((S)-2-amino-3,3-dimethylbutanoyl)-N-((S)-1-amino-3-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)-1-oxopropan-2-yl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

[000452] A mixture of tert-butyl N-[(1S)-1-[(1R,2S,5S)-2-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carbonyl]-2,2-dimethyl-propyl]carbamate (0.5 g, 909.59 umol, 1 eq) in HCl/EtOAc (4 M, 200 mL, 879.52 eq) was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. Then the mixture was dissolved in toluene (10 mL) and concentrated under reduced pressure for two times to give (1R,2S,5S)-3-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (540 mg, crude, HCl) as a white solid and used directly for next step. MS (ESI) *m/z* 450.3 $[M+H]^+$

Step 5: (1R,2S,5S)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopiperidin-3-yl)propan-2-yl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

[000453] To a solution of (1R,2S,5S)-3-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (0.44 g, 905.26 umol, 1 *eq*, HCl) in DCM (10 mL) was added DIEA (351.00 mg, 2.72 mmol, 473.04 uL, 3 *eq*), and cooled to 0 °C, then added TFAA (152.11 mg, 724.21 umol, 100.73 uL, 0.8 *eq*). The mixture was stirred at 0 °C for 1 h. Upon completion, the combined reaction mixture was poured into aq.$NaHCO_3$ (20 mL) and extracted with DCM (10 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (1R,2S,5S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (350 mg, crude, 70.86% yield) as a white solid and used directly for next step. MS (ESI) *m/z* 546.1 $[M+H]^+$

Step 6: (1R,2S,5S)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

[000454] To a solution of (1R,2S,5S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (0.3 g, 549.86 umol, 1 eq) in DCM (5 mL) was added burgess reagent (393.10 mg, 1.65 mmol, 3 eq). The mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was quenched by water (0.5 mL) at 20 °C, and the system was blow-dried with N_2 to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30 mm *10 um; mobile phase: [water(10 mM NH_4HCO_3) - ACN]; B%: 35% - 60%, 8min) to give (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (91.51 mg, 173.45 umol, 31.54% yield, 100% purity) as a white solid. MS (ESI) *m/z* 528.2 $[M+H]^+$

[000455] ^{1}H NMR (400MHz, DMSO-d_6) δ = 9.41 (br d, *J* = 7.7 Hz, 1H), 8.99 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 4.97 - 4.88 (m, 1H), 4.40 (br d, *J* = 7.1 Hz, 1H), 4.20 - 4.14 (m, 1H), 3.90 (br dd, *J* = 5.5, 10.4 Hz, 1H), 3.68 (br d, *J* = 10.6 Hz, 1H), 2.21 - 2.08 (m, 2H), 1.99 (br dd, *J* = 8.8, 12.3 Hz, 1H), 1.75 (ddd, *J* = 5.7, 10.3, 13.5 Hz, 1H), 1.59 - 1.51 (m, 2H), 1.29 (d, *J* = 7.7 Hz, 1H), 1.20 - 1.16 (m, 3H), 1.10 (s, 3H), 1.05 - 1.01 (m, 3H), 1.01 - 0.95 (m, 9H), 0.86 - 0.83 (m, 3H)

[000456] Step 7: (1R,2S,5S)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

[000457] The (1R,2S,5S)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide was further separated by SFC (column: DAICEL CHIRALPAK AD-H(250 mm * 30 mm, 5 um); mobile phase: [Neu-IPA]; B%: 5%-15%,15min) to give (1R,2S,5S)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-

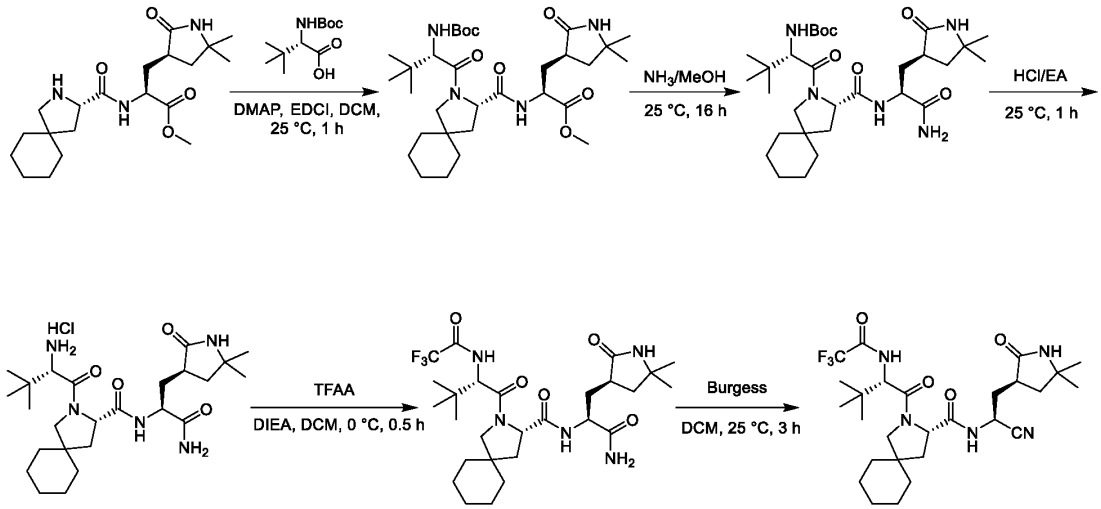
6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide Isomer 1 (5.1 mg, 9.67 umol, 5.74% yield) as a white solid. MS (ESI) *m/z* 528.2 $[M+H]^+$

[000458] ^{1}H NMR (400MHz, DMSO-d_6) δ = 9.50 - 9.36 (m, 1H), 9.09 - 8.96 (m, 1H), 7.98 - 7.82 (m, 1H), 4.98 - 4.87 (m, 1H), 4.40 (br d, *J* = 5.5 Hz, 1H), 4.21 - 4.15 (m, 1H), 3.97 - 3.85 (m, 1H), 3.73 - 3.60 (m, 1H), 2.53 - 2.52 (m, 1H), 2.15 - 2.08 (m, 1H), 2.07 - 1.93 (m, 1H), 1.84 - 1.70 (m, 1H), 1.58 - 1.47 (m, 2H), 1.35 - 1.27 (m, 1H), 1.22 - 1.17 (m, 3H), 1.16 - 1.08 (m, 3H), 1.05 - 1.00 (m, 3H), 1.00 - 0.94 (m, 9H), 0.86 - 0.81 (m, 3H).

[000459] To give (1R,2S,5S)-N-((S)-1-cyano-2-((R)-5,5-dimethyl-2-oxopyrrolidin-3-yl)ethyl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide Isomer 2 (61.8 mg, 117.14 umol, 69.59% yield) as a white solid. MS (ESI) *m/z* 528.2 $[M+H]^+$

[000460] ^{1}H NMR (400MHz, DMSO-d$_6$) δ = 9.41 (br d, *J* = 7.7 Hz, 1H), 8.99 (br d, *J* = 8.2 Hz, 1H), 7.84 (s, 1H), 4.96 - 4.89 (m, 1H), 4.40 (br d, *J* = 7.1 Hz, 1H), 4.17 (s, 1H), 3.90 (br dd, *J* = 5.4, 10.5 Hz, 1H), 3.68 (br d, *J* = 10.6 Hz, 1H), 2.52 (d, *J* = 2.0 Hz, 1H), 2.19 - 2.10 (m, 1H), 1.99 (br dd, *J* = 8.7, 12.5 Hz, 1H), 1.75 (ddd, *J* = 5.6, 10.1, 13.3 Hz, 1H), 1.59 - 1.51 (m, 2H), 1.29 (d, *J* = 7.7 Hz, 1H), 1.19 - 1.16 (m, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.98 (s, 9H), 0.86 - 0.84 (m, 3H)

Example 312. Synthesis of viral protease inhibitor compound 3073



Step 1: methyl (2S)-2-[[(3S)-2-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-2-azaspiro [4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate

[000461] To a mixture of methyl (2S)-2-[[(3S)-2-azaspiro[4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (200 mg, 480.82 umol, 1 *eq*, HCl) in DCM (10 mL) was added DMAP (117.48 mg, 961.65 umol, 2 *eq*), (2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoic acid (111.21 mg, 480.82 umol, 1 *eq*) and EDCI (184.35 mg, 961.65 umol, 2 *eq*) at 25 °C.The mixture was stirred at 25 °C for 60 min. Upon completion, the reaction mixture was diluted with H_2O 20 mL and extracted with EA 50 mL (25 mL * 2). The combined organic layers were washed with brine 25 mL (25 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1) to get the crude 180 mg. The residue was purified by neutral condition prep-HPLC. (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 50%-80%,10min). Compound methyl (2S)-2-[[(3S)-2-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-2-azaspiro [4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (70 mg, 118.09 umol, 24.56% yield, 100% purity) was obtained as a white solid. MS (ESI) *m/z* 593.4 $[M+H]^+$

Step2: tert-butyl N-[(1S)-1-[(3S)-3-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl] -2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carbonyl]-2,2-dimethyl-propyl]carbamate

[000462] Methyl (2S)-2-[[(3S)-2-[(2S)-2-(tert-butoxycarbonylamino)-3,3-dimethyl-butanoyl]-2-azaspiro [4.5]decane-3-carbonyl]amino]-3-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]propanoate (70 mg, 118.09 umol, 1 *eq*) was added NH_3/MeOH (7 M, 14.00 mL, 829.87 *eq*). The mixture was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was used next step directly. Compound tert-butyl N-[(1S)-1-[(3S)-3-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carbonyl]-2,2-dimethyl-propyl]carbamate (68 mg, 115.34

umol, 97.67% yield, 98% purity) was obtained as a white solid. MS (ESI) *m/z* 578.4 $[M+H]^+$

Step 3: (3S)-2-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-azaspiro[4.5]decane-3-carboxamide

[000463] Tert-butyl N-[(1S)-1-[(3S)-3-[[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]- 2-oxo-ethyl]carbamoyl]-2-azaspiro[4.5]decane-2-carbonyl]-2,2-dimethyl-propyl]carbamate (68 mg, 117.70 umol, 1 *eq*) was added HCl/EtOAc (4 M, 3.78 mL, 128.39 *eq*). The mixture was stirred at 25 °C for 60 min. Upon completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was used next step directly. Compound (3S)-2-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-azaspiro[4.5]decane-3-carboxamide (60 mg, 114.37 umol, 97.18% yield, 98% purity, HCl) was obtained as a white solid.

Step 4: (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-[(2S) -3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-2-azaspiro[4.5]decane-3-carboxamide

[000464] (3S)-2-[(2S)-2-amino-3,3-dimethyl-butanoyl]-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-azaspiro[4.5]decane-3-carboxamide (40 mg, 77.81 umol, 1 eq, HCl) in DCM (4 mL) was added DIEA (30.17 mg, 233.42 umol, 40.66 uL, 3 eq) and TFAA (19.61 mg, 93.37 umol, 12.99 uL, 1.2 eq) at 0 °C, the mixture was stirred at 0 °C for 30 min. Upon completion, the reaction mixture was quenched by addition H_2O 2 mL at 0 °C, and extracted with EA 10 mL (5 mL * 2). The combined organic layers were washed with brine 5 mL (5 mL * 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue and used next step directly. Compound (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-2-azaspiro[4.5]decane-3-carboxamide (60 mg, 73.22 umol, 94.10% yield, 70% purity) was obtained as a white solid. MS (ESI) *m/z* 574.2 $[M+H]^+$

Step 5: (3S)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]ethyl]-2-[(2S)-3,3-dimethyl -2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-2-azaspiro[4.5]decane-3-carboxamide

[000465] To a mixture of (3S)-N-[(1S)-2-amino-1-[[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl]methyl]-2-oxo-ethyl]-2-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-2-azaspiro[4.5]decane-3-carboxamide (30 mg, 52.30 umol, 1 *eq*) in DCM (3 mL) was added BURGESS REAGENT (24.93 mg, 104.59 umol, 2 *eq*). The mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was diluted with H_2O 5 mL and extracted with DCM 10 mL (5 mL * 2). The combined organic layers were concentrated by blow-drying to give a residue. The residue was purified by neutral condition prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [water (10mM NH4HCO3)-ACN]; B%: 40%-70%, 10 min). Compound (3S)-N-[(1S)-1-cyano-2-[(3R)-5,5-dimethyl-2-oxo-pyrrolidin-3-yl] ethyl]-2-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-2-azaspiro[4.5]decane-3-carboxamide (10 mg, 17.40 umol, 33.28% yield, 96.7% purity) was obtained as a white solid. MS (ESI) *m/z* 556.2 $[M+H]^+$

[000466] ^{1}H NMR (400 MHz, DMSO-*d*6) δ = 8.98 - 8.29 (m, 2H), 7.50 (br s, 1H), 5.01 - 4.78 (m, 1H), 4.56 (s, 1H), 4.31 (br t, *J* = 8.6 Hz, 1H), 3.79 (br d, *J* = 10.1 Hz, 1H), 3.29 (br d, *J* = 10.0 Hz, 1H), 2.60 (br dd, *J* = 5.4, 8.9 Hz, 1H), 2.26 - 2.03 (m, 3H), 1.87 - 1.71 (m, 1H), 1.64 - 1.26 (m, 12H), 1.25 - 1.13 (m, 6H), 1.03 (s, 9H)

Example 313. Evaluation of antiviral activity of Compounds against COVID-19 (nCoV-2019, SARS-CoV2) Mpro in the enzymatic assay

[0002027] Compounds are assayed using standard methods to assess compound activity and IC50. As an exemplary for assessment of the SARS-COV2 Mpro, the C-His6-tagged Mpro (NC_045512) is cloned, expressed in E. coli and purified. The assay buffer contains 20 mM of Tris-HCl (pH 7.3), 100 mM of NaCl, 1 mM of EDTA, 5mM of TCEP and 0.1%BSA. The final concentrations of the Mpro protein and substrate are 25 nM and 25 μM, respectively, in the Mpro enzymatic assay. The Km of the Mpro substrate for the protease was 13.5 μM.

[0002028] The compounds are added to an assay plate. For 100% inhibition control (HPE, hundred percent effect), 1 μM GC376 is added. For no inhibition control (ZPE, zero

percent effect), no compound is added. Each activity testing point has a relevant background control to normalize the fluorescence interference of compound.

[0002029] IC50 values of compounds are calculated with the GraphPad Prism software using the nonlinear regression model of log(inhibitor) vs. response -- Variable slope (four parameters). The inhibition activity is calculated using the formula below, IC50 values is calculated using the Inhibition% data.

*Inhibition% =[(Sample- Average ZPE)/(Average HPE-Average ZPE)] * 100%* [#]

[#] *HEP: Hundred percent effect controls. Containing substrate + enzyme + 1 μM GC376.*

ZPE: Zero percent effective controls. Containing enzyme + substrate, no compound.

Sample: Compound activity testing wells. Containing compound + enzyme + substrate.

BG: Compound background control wells. Containing compound + substrate, no enzyme.

Example 314. Evaluation of antiviral activity of Compounds against human coronavirus (HCov) 229E and OC43 in the cytopathic effect (CPE) assays

[0002030] Compounds are assayed using standard methods against multiple coronaviral strains, including HCoV 229E and OC43 strains. The antiviral activity of compounds is calculated based on the protection of the virus-induced CPE at each concentration normalized by the virus control.

[0002031] Reagents and instruments used in this assay include luminescent cell viability assay kit CellTiter Glo (Promega) and Microplate Reader Synergy2 (BioTek).

Virus - HCoV 229E

[0002032] Cytopathic effect (CPE) is measured by CellTiter Glo following the manufacturer's manual. The antiviral activity of compounds is calculated based on the protection of the virus-induced CPE at each concentration normalized by the virus control.

Virus - HCov OC43

[0002033] Reference compound used is remdesivir; detection reagent: CellTiter Glo.) The CPE are measured by CellTiter Glo following the manufacturer's manual. The antiviral activity of compounds is calculated based on the protection of the virus-induced CPE at each concentration normalized by the virus control.

[0002034] The cytotoxicity of compounds is assessed under the same conditions, but without virus infection, in parallel. Cell viability is measured with CellTiter Glo. The antiviral activity and cytotoxicity of compounds are expressed as % Inhibition and % Viability, respectively, and calculated with formulas.

[0002035] Table 3, Table 4 and Table 5 show activity data.

Table 3. Activity data for compounds.

Compound No.	229E Mpro EC_{50}	SARS-CoV2 Mpro IC_{50}
101	D	D
103	D	D
127	B	C
129	C	D
131	D	D
133	D	D
134	D	D
134 (Isomer 1)	D	D
134 (Isomer 2)	D	D
135	D	D
135 (Isomer 1)	C	C
135 (Isomer 2)	D	D
136	D	D
143	C	C
145	D	D
147	A	D
149	C	D
153	B	D
163	B	C
165	A	B
167	C	D
171	D	D
183	C	D
185	D	D
191	A	C
197	D	D
199	A	B
201	C	C
205	D	D
209	C	C
213	A	B
223 (Isomer 1)	B	B
223 (Isomer 2)	A	A
225	A	A
227	A	C
231	A	A
237	A	A
241	A	A
245	A	C
249	A	A

253	C	C
265	C	C
267	D	D
267A	A	A
269	A	A
269	A	A
271	A	A
271A (Isomer 1)	A	A
271A (Isomer 2)	A	A
271A (Isomer 3)	A	A
271A (Isomer 4)	A	A
273A	A	A
273B	A	A
273C	C	A
279	A	A
305	D	D
323 (Isomer 1)	D	D
323 (Isomer 2)	D	D
325	B	B
327	D	D
329	D	D
331 (Isomer 1)	D	D
331 (Isomer 2)	D	D
344D	D	D
344C	D	D
344A	D	D
345	D	D
345 (Isomer 1)	D	D
345 (Isomer 2)	D	D
355	C	D
357	A	B
359	B	C
361	D	D
363	D	D

365 (Isomer 1)	C	D
365 (Isomer 2)	C	B
369 (Isomer 1)	B	C
369 (Isomer 2)	C	C
375A	D	D
377	D	D
379	D	D
383	C	C
385 (Isomer 1)	D	D
385 (Isomer 2)	D	C
387	A	B
389A (Isomer 1)	D	D
391	A	A
393	D	D
395 (Isomer 1)	D	D
395 (Isomer 2)	D	D
397	D	D
399 (Isomer 1)	D	C
399A (Isomer 1)	D	D
399A (Isomer 2)	B	A
401	D	D
401 (Isomer 1)	D	D
401 (Isomer 2)	C	C
405	D	D
407	D	C
409	A	C
413	D	C
429A (Isomer 1)	A	B
429A (Isomer 2)	A	A
431	B	B
433	D	D
439	A	B
449	B	B
449 (Isomer 1)	A	A

449 (Isomer 2)	B	C
451 (Isomer 1)	A	A
451 (Isomer 2)	B	C
455	A	A
457	A	A
459	A	A
465	B	B
465 (Isomer 1)	A	A
465 (Isomer 2)	B	C
467 (Isomer 1)	C	C
467 (Isomer 2)	A	A
469	A	B
469 (Isomer 1& Isomer 2)	A	A
469 (Isomer 3)	A	A
469 (Isomer 4)	A	A
471	B	A
473 (Isomer 1)	A	A
473 (Isomer 2)	A	A
475 (Isomer 1 & Isomer 2)	C	B
475 (Isomer 3)	B	A
475 (Isomer 4)	A	A
477	A	B
479	B	A
481 (Isomer 1)	A	A
481 (Isomer 2)	A	A
483	A	A
483 (Isomer 1)	A	A
483 (Isomer 2)	A	A
489 (Isomer 1)	A	A
489 (Isomer 2)	A	A
491	D	D
491 (Isomer 1)	D	D

491 (Isomer 2)	A	B
491 (Isomer 4)	D	D
491A (Isomer 1)	A	A
491A (Isomer 2)	D	D
491B	B	B
493	A	A
495 (Isomer 1)	A	A
495 (Isomer 2)	A	A
497 (Isomer 2)	D	D
499	D	D
501	A	A
505 (Isomer 1)	A	A
505 (Isomer 2)	A	C
507 (Isomer 1.1)	D	D
507 (Isomer 1.2)	D	D
507 (Isomer 2.1)	D	D
507 (Isomer 2.2)	D	D
509	D	D
511	D	D
511 (Isomer 1)	D	D
511 (Isomer 2)	D	D
513 (Isomer 1)	C	C
513 (Isomer 2)	C	D
515	D	D
519	D	D
525	D	D
529	D	D
531	D	D
535	A	C
547 (Isomer 2)	D	C
549	D	D
551	D	D
555	B	B

577	D	D
581	A	B
583	A	B
591 (Isomer 1)	A	A
591 (Isomer 2)	A	C
595	D	D
598	C	D
603a (Isomer 1)	D	D
603a (Isomer 2)	A	B
611	D	D
619	D	D
621	D	D
623	A	A
625	D	D
633	D	D
635	D	D
637	D	D
639	D	D
639A	D	D
643	D	D
647	D	D
649	C	C
653 (Isomer 1)	D	D
653 (Isomer 2)	D	D
655	B	A
659	A	A
667	D	D
669	D	D
671	B	C
681 (Isomer 1)	D	D
691	D	D
695	D	D
711	D	D
715	D	D

717	D	D
719 (Isomer 2)	D	D
719A (Isomer 1)	B	B
721	D	D
723 (Isomer 1)	B	B
723 (Isomer 2)	D	D
725	D	D
727	D	D
729 (Isomer 1)	D	D
729 (Isomer 2)	D	C
731 (Isomer 1)	D	D
731 (Isomer 2)	B	C
733 (Isomer 1)	D	D
733 (Isomer 2)	C	C
735	D	D
737	D	D
739	D	D
740	B	C
741	D	D
743 (Isomer 1)	A	A
743 (Isomer 2)	D	D
745	D	D
747	D	D
749A (Isomer 1)	C	D
749A (Isomer 2)	C	D
787A (Isomer 1)	C	D
787A (Isomer 2)	C	D
791 (Isomer 1)	A	A
791 (Isomer 2)	D	D
793	D	D
795	D	D
799	D	D
801 (Isomer 1)	D	D
801 (Isomer 2)	B	B

803 (Isomer 1)	A	A
803 (Isomer 2)	A	A
803 (Isomer 3)	D	D
803 (Isomer 4)	D	C
805 (Isomer 1)	A	B
805 (Isomer 2)	D	D
808	D	D
810	D	D
812	D	D
814 (Isomer 1)	A	A
814 (Isomer 2)	D	D
816	A	A
820	D	D
822	D	D
824	D	D
826	D	D
828	D	D
830	D	D
832	D	D
838	D	D
840	D	D
842	D	D
846	D	D
848	D	D
850	B	D
852	D	D
854	D	D
856	D	D
858	D	D
860	D	D
862	D	D
864	D	D
866	D	D
868	D	D

872	C	C
875 (Isomer 1)	D	D
875 (Isomer 2)	D	D
875 (Isomer 3)	B	B
876	D	D
878 (Isomer 1)	D	D
878 (Isomer 2)	B	A
880 (Isomer 1)	B	A
880 (Isomer 2)	D	D
882 (Isomer 1)	D	D
882 (Isomer 2)	B	B
886 (Isomer 1)	A	A
886 (Isomer 2)	D	D
888	D	D
892	D	D
894	D	D
896 (Isomer 1)	D	D
896 (Isomer 2)	A	A
898	D	D
900	D	D
902 (Isomer 1)	D	D
902 (Isomer 2)	B	C
902 (Isomer 3)	D	D
902 (Isomer 4)	A	A
906	D	D
908 (Isomer 1)	D	D
908 (Isomer 2)	C	C
928 (Isomer 3)	C	D
928 (Isomer 4)	A	C
930 (Isomer 1)	A	B
930 (Isomer 2)	A	B
930 (Isomer 3)	D	D
930 (Isomer 3.1)	D	D
930 (Isomer 3.2)	B	C

930 (Isomer 4)	B	C
930 (Isomer 5)	A	B
930 (Isomer 6)	D	D
932	D	D
982 (Isomer 1)	D	D
982 (Isomer 2)	A	A
984 (Isomer 1)	D	D
984 (Isomer 2)	A	B
986 (Isomer 1)	D	D
986 (Isomer 2)	A	A
988 (Isomer 1)	A	A
988 (Isomer 2)	D	D
990 (Isomer 1)	A	A
990 (Isomer 2)	D	D
992 (Isomer 1)	D	D
992 (Isomer 2)	A	A
1057	D	D
1137	C	D
1149	D	D
1258	C	C
1053 (Isomer 1)	A	C
1053 (Isomer 2)	B	C
1053 (Isomer 3)	C	D
1053 (Isomer 4)	D	D
1055 (Isomer 1)	A	A
1055 (Isomer 2)	A	A
1059 (Isomer 1)	D	D

1059 (Isomer 2)	B	B
1111 (Isomer 1)	C	D
1111 (Isomer 2)	A	A
1111 (Isomer 3)	C	D
1111 (Isomer 4)	A	A
1147A (Isomer 1)	D	D
1147A (Isomer 2)	B	C
3069	A	D
3133	D	D
3129	D	D
3065	A	D
3071a (Isomer 1)	C	D
3071a (Isomer 2)	A	A
3075	B	D
3073	C	D
3041	D	D
3045	D	D
3075 (Isomer 1)	A	D
3075 (Isomer 2)	B	D
3037	D	D
3039a (Isomer 1)	C	D
3039b	D	D
3043	D	D
3135	D	D
3131	B	D

A ≥30 μM, B > 10 μM and <30 μM, C ≥2 μM and ≤10 μM, D <2 μM.

Table 4. Activity data for compounds.

Compound No.	**229E CPE EC_{50} (μM)**
101	D
103	D
127	C
131	C

133	D
134	D
134 (Isomer 1)	D
134 (Isomer 2)	D
135	D
135 (Isomer 2)	D
136	A
149	C
171	D
185	D
197	D
205	D
323 (Isomer 1)	D
323 (Isomer 2)	D
327	C
329	D
331 (Isomer 1)	D
331 (Isomer 2)	D
344D	D
344C	D
344A	D
345	D
345 (Isomer 1)	D
345 (Isomer 2)	D
355	A
361	D
363	D
375A	D
377	D
379	D
385 (Isomer 1)	D
385 (Isomer 2)	D
389A (Isomer 1)	D
393	D
397	D
399 (Isomer 1)	D
401	D

401 (Isomer 1)	D
405	D
407	D
433	C
491	D
497 (Isomer 2)	D
507 (Isomer 1.1)	D
507 (Isomer 1.2)	D
507 (Isomer 2.1)	D
507 (Isomer 2.2)	D
509	D
511	D
511 (Isomer 1)	D
511 (Isomer 2)	D
513 (Isomer 2)	C
519	D
531	D
551	C
577	D
598	D
635	D
637	D
639	D
643	D
653	D
681 (Isomer 1)	D
711	D
715	D
717	D
719 (Isomer 2)	D
721	D
723 (Isomer 2)	D
725	D
729 (Isomer 1)	D
731 (Isomer 1)	D
733 (Isomer 1)	D

735	D
737	D
739	D

743 (Isomer 2)	D
745	D
747	D

A > 30 μM, B > 10 μM and ≤30 μM, C ≥2 μM and ≤10 μM, D <2 μM.

Table 5. Activity data for compounds.

Compound No.	229E CC_{50}
130 (Isomer 1)	A
135	A
170	A

A > 30 μM, B > 10 μM and ≤30 μM, C ≥2 μM and ≤10 μM, D <2 μM.

INCORPORATION BY REFERENCE

[0002036] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

[0002037] While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

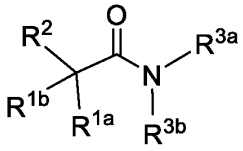
[0002038] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims

are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

CLAIMS

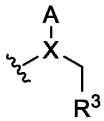
What is claimed is:

1. A protease inhibitor compound represented by:



Formula II,

or a pharmaceutically acceptable salt, stereoisomer, ester, or prodrug thereof, wherein:

R^{3a} is selected from  and 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_1-C_8alkoxy, oxo and a warhead A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl; wherein R^{3a} and R^{3b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle, wherein the heterocycle may optionally be substituted by one, two or three substituents each independently selected from C_6-C_{14}aryl and a warhead A;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, $-CH_2CF_3$, $-CF_3$, $-O-CF_3$, $-O-CHF_2$, $-S-CH_3$, $-S(O)_2-CH_3$, $-NH_2$, $-O$-phenyl, $-O-(C_1-C_8alkyl)$-phenyl, $-NHC(O)R^B$, $-NHC(O)OR^B$, $-NHC(O)O-(C_1-C_8alkyl)-R^B$, $-N(R^y)_2$, $-N(R^y)(C_1-C_8alkyl)C(O)O$-phenyl, $-N(R^y)(C_1-C_8alkyl)C(O)N(R^y)_2$, $-C(O)-OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, $-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, $-(C_1-C_8alkyl)-(C_6-C_{14}aryl)$, $-(C_1-C_8alkyl)$-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, $-NH_2$, hydroxyl and oxo;

R^2 is selected from the group consisting of $-NHC(O)R^B$, $-NHC(O)OR^B$, $-NHC(O)N(R^B)_2$, $-NHC(O)C(R^C)_2R^B$, $-NHS(O)_2R^B$, $-O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl)$, 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered monocyclic or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^3 is selected from 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^3 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, -O-C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and

wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl;

R^G is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-$C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-$C_{3\text{-}6}$cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{ii};

R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -NH(C=O)R^m;

R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, $-NR^mR^m$, $-NR^m(C=O)R^m$, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy;

R^{jj} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2;

R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, $-S(O)_2-CH_3$, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo;

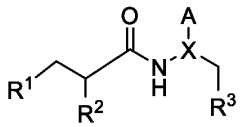
R^{xx} is $–(OCH_2CH_2)_{nn}–$, wherein nn is selected from 1, 2, 3, 4, 5 and 6;

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, $–CF_3$, $–CH_2CF_3$, C_1-C_8alkoxy,–(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH;

A is a warhead; and

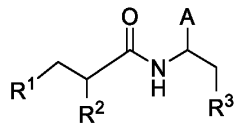
X is selected from the group consisting of $C(R^{xy})$ and N, wherein R^{xy} is selected from the group consisting of H, D, -OH, $-NH_2$, halogen, C_1-C_8alkyl, C_1-C_8 haloalkyl, and C_1-C_8alkoxy.

2. The compound of claim 1, wherein the compound is represented by:



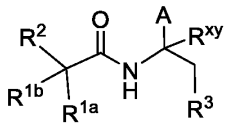
Formula II-A.

3. The compound of claim 1, wherein the compound is represented by:



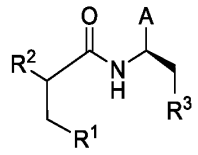
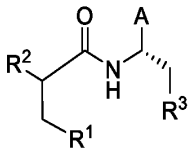
Formula II-B.

4. The compound of claim 1, wherein the compound is represented by:

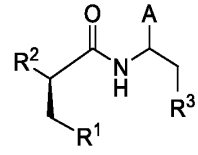
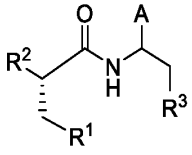


Formula II-C.

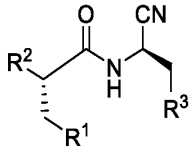
5. The compound of claim 1, wherein the compound is represented by:

 (Formula II-D-A) or  (Formula II-D-B).

6. The compound of claim 1, wherein the compound is represented by:

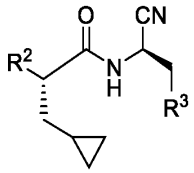
 (Formula II-E-A) or  (Formula II-E-B).

7. The compound of claim 1, wherein the compound is represented by:



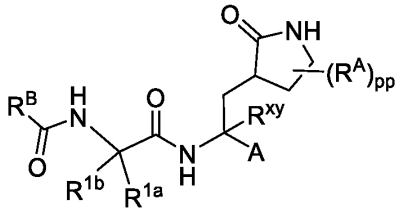
Formula II-F.

8. The compound of claim 1, wherein the compound is represented by:

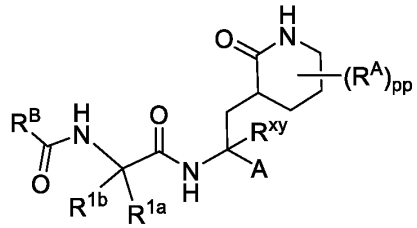


Formula II-G.

9. The compound of claim 1, wherein the compound is represented by:



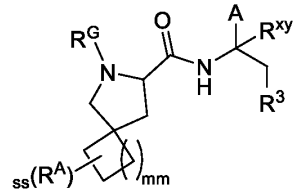
(Formula II-D-I), or



(Formula II-D-II),

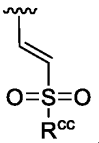
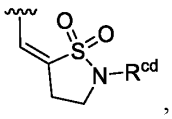
wherein pp is selected from 0, 1, 2, and 3.

10. The compound of claim 1, wherein the compound is represented by:



(Formula II-E-II),

wherein ss is selected from 0, 1, 2, and 3, and mm is selected from 1, 2, and 3.

11. The compound of any one of claims 1-6, 9 and 10, wherein A is selected from the group consisting of cyano, $-C(O)R^D$, $-C(O)CH_2N(R^bR^c)$, $-C(O)CH_2OC(O)R^D$, $-C(O)C(O)R^D$, $-(CH=CH)C(O)OR^D$, $-(CH=CCN)C(O)OR^D$, $-(CH=CCN)C(O)(NH)R^D$, $-CH(CN)(OH)$, $-CH(CN)(NR^bR^c)$,  , and  , wherein

R^D is selected from the group consisting of hydrogen, hydroxyl, $-OR^{bb}$, $-N(R^bR^c)$, C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle; wherein R^D may optionally be substituted

by one, two, or three substituents each independently selected from the group consisting of halogen, hydroxyl, and R^E;

R^E is independently selected for each occurrence from the group consisting of C_1-C_8alkyl, C_1-C_8alkoxy, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl, wherein R^E may optionally be substituted by one, two, or three substituents each independently selected from the group consisting of halogen, cyano, C_1-C_8alkyl and C_1-C_8alkoxy;

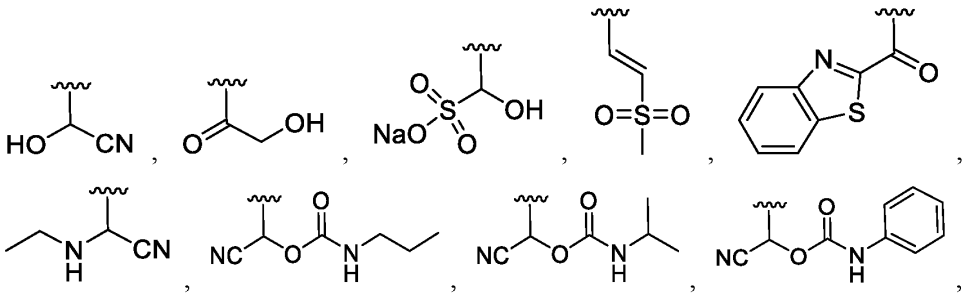
R^{bb} is selected from the group consisting of C_3-C_6cycloalkyl, C_6-C_{14}aryl, -(C_1-C_8alkyl)-C_6-C_{14}aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycle;

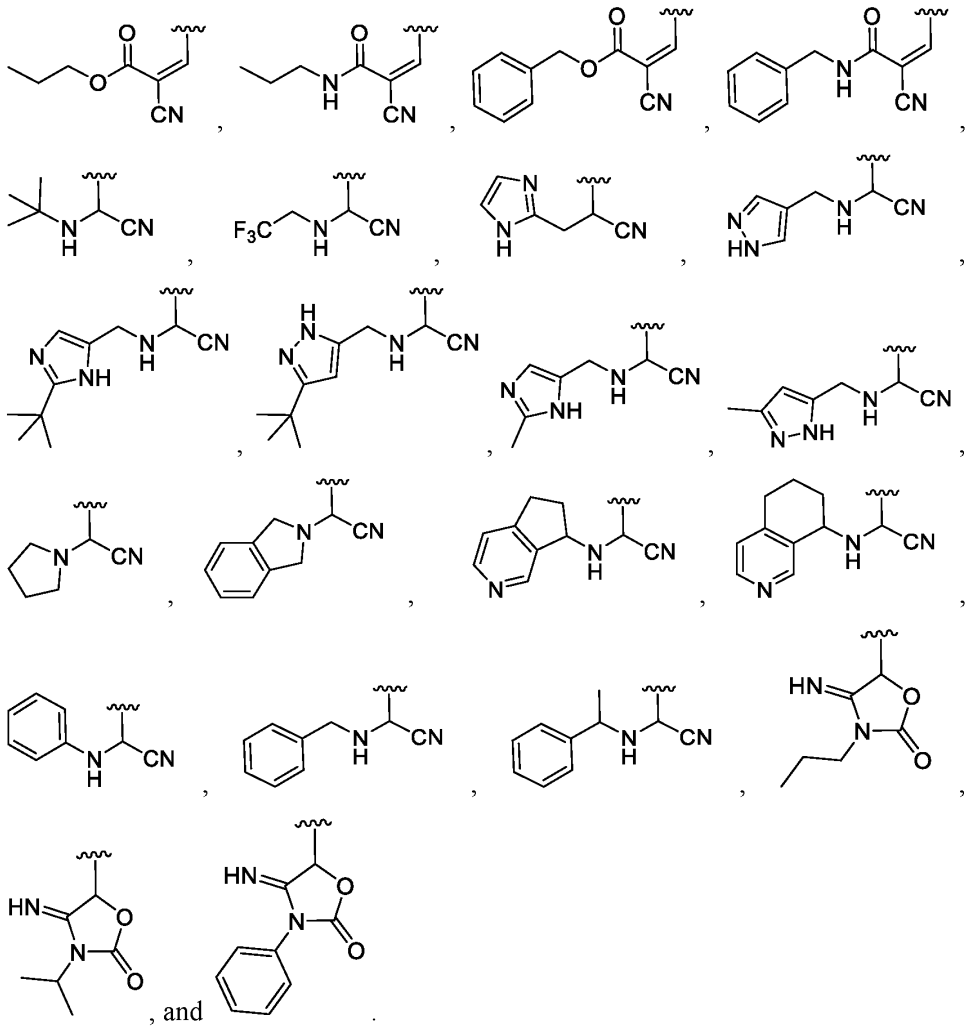
R^{cc} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_3-C_6cycloalkyl, -(C_1-C_8alkyl)-(C_6-C_{14}aryl), C_6-C_{14}aryl, 5-10 membered heteroaryl, -(C_1-C_8alkyl)-(5-10 membered heteroaryl), 5-10 membered heterocycle and -N(R^bR^c), wherein R^b and R^c are each independently selected from the group consisting of hydrogen, C1-C_8alkyl, and C_3-C_6cycloalkyl, or R^b and R^c may be joined together to form, together with the nitrogen to which they are attached, a 5-10 membered heterocycle;

R^{cd} is selected from the group consisting of hydrogen, C_1-C_8alkyl, and C_3-C_6cycloalkyl; and

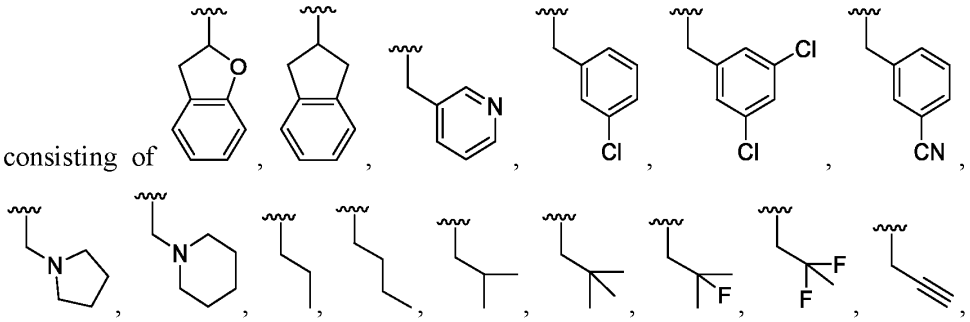
R^b and R^c are each selected from the group consisting of hydrogen, –$CH_2C(O)O(C_1$-C_8alkyl), –C(O)-(C_1-C_8alkyl), –$S(O)_2$-(C_1-C_8alkyl), C_1-C_8alkyl, C_3-C_6cycloalkyl and -(C_1-C_8alkyl)-C_6-C_{14}aryl, wherein the C_1-C_8alkyl may optionally be substituted by one or more substituents each independently selected from the group consisting of halogen, C_3-C_6cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle, and 5-10 membered heteroaryl.

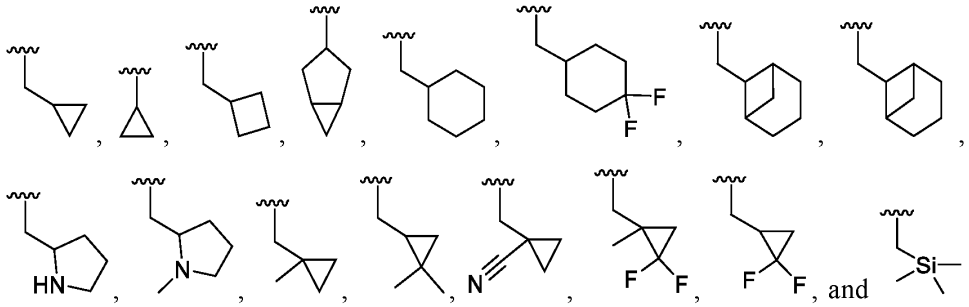
12. The compound of claim 11, wherein A is selected from the group consisting of -CN,





13. The compound of any one of claims 1, 4 and 9, wherein R^{1a} is selected from the group consisting of



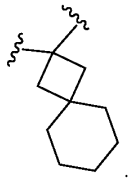


.

14. The compound of any one of claims 1, 4, and 9, wherein R^{1a} is $-(C_1\text{-}C_8\text{alkyl})\text{-}R^1$.

15. The compound of any one of claims 1, 4 and 9, wherein R^{1b} is hydrogen.

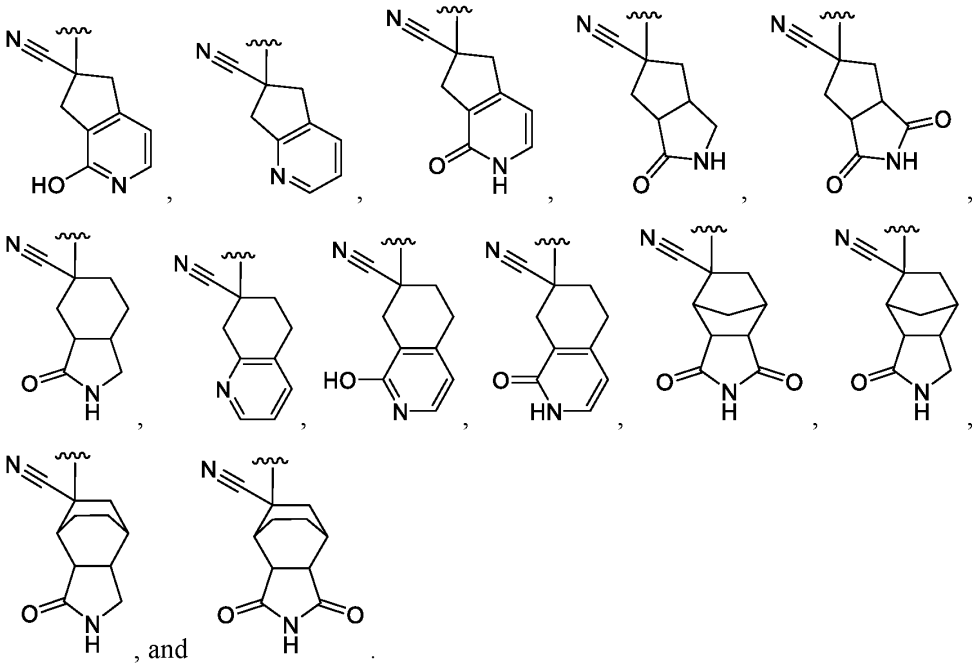
16. The compound of claim 1, wherein R^{1a} and R^{1b} are joined to together to form



.

17. The compound of claim 1, wherein R^{3a} is a 4-10 membered heterocycle substituted by A.

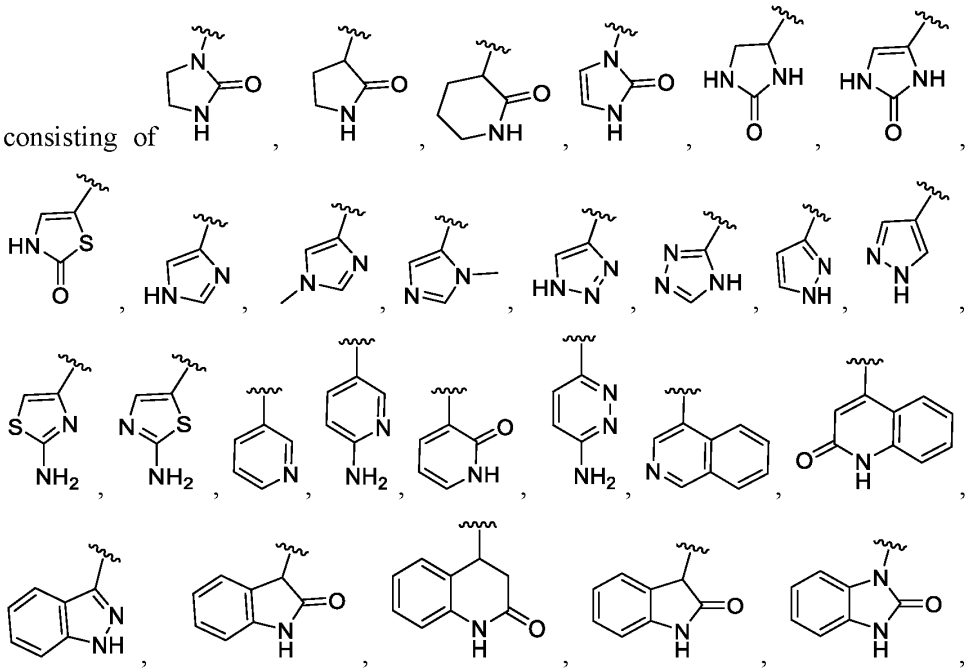
18. The compound of claim 1, wherein R^{3a} is selected from the group consisting of

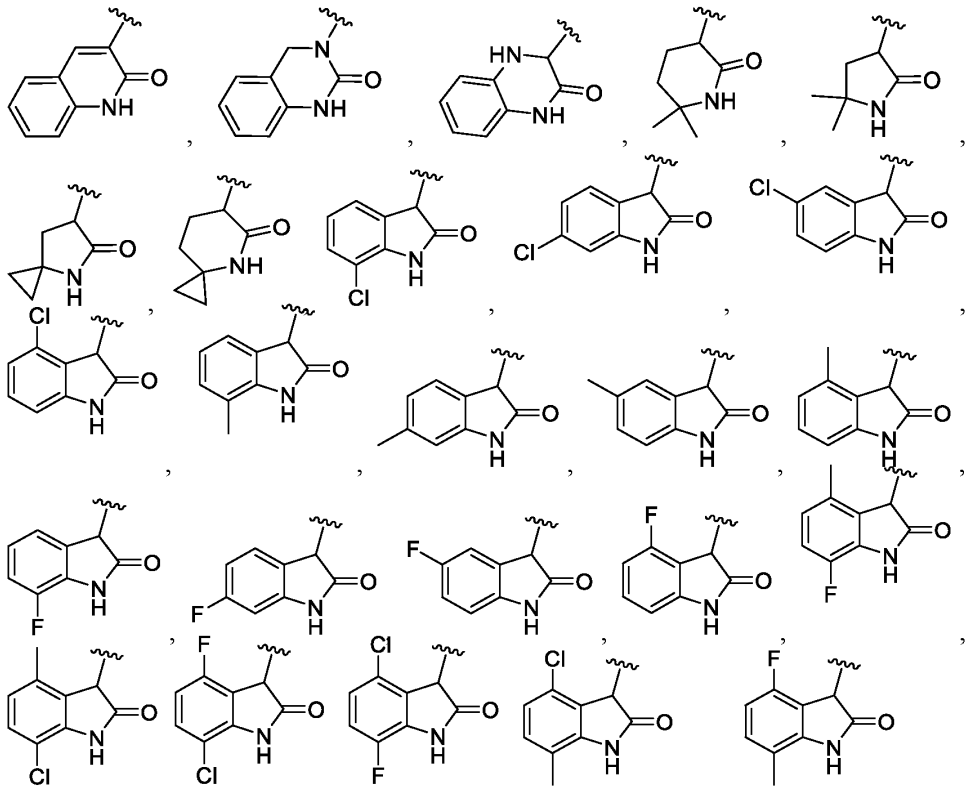


, and .

19. The compound of any one of claims 1-8, wherein R^3 is a 4-10 membered heterocycle.

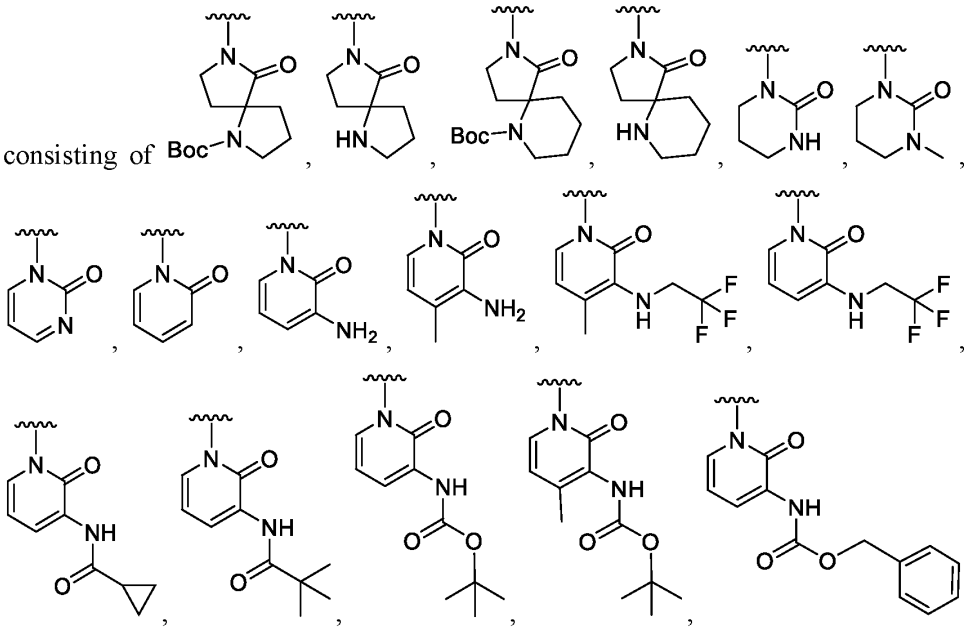
20. The compound of any one of claims 1-8 and 10, wherein R^3 is selected from the group consisting of

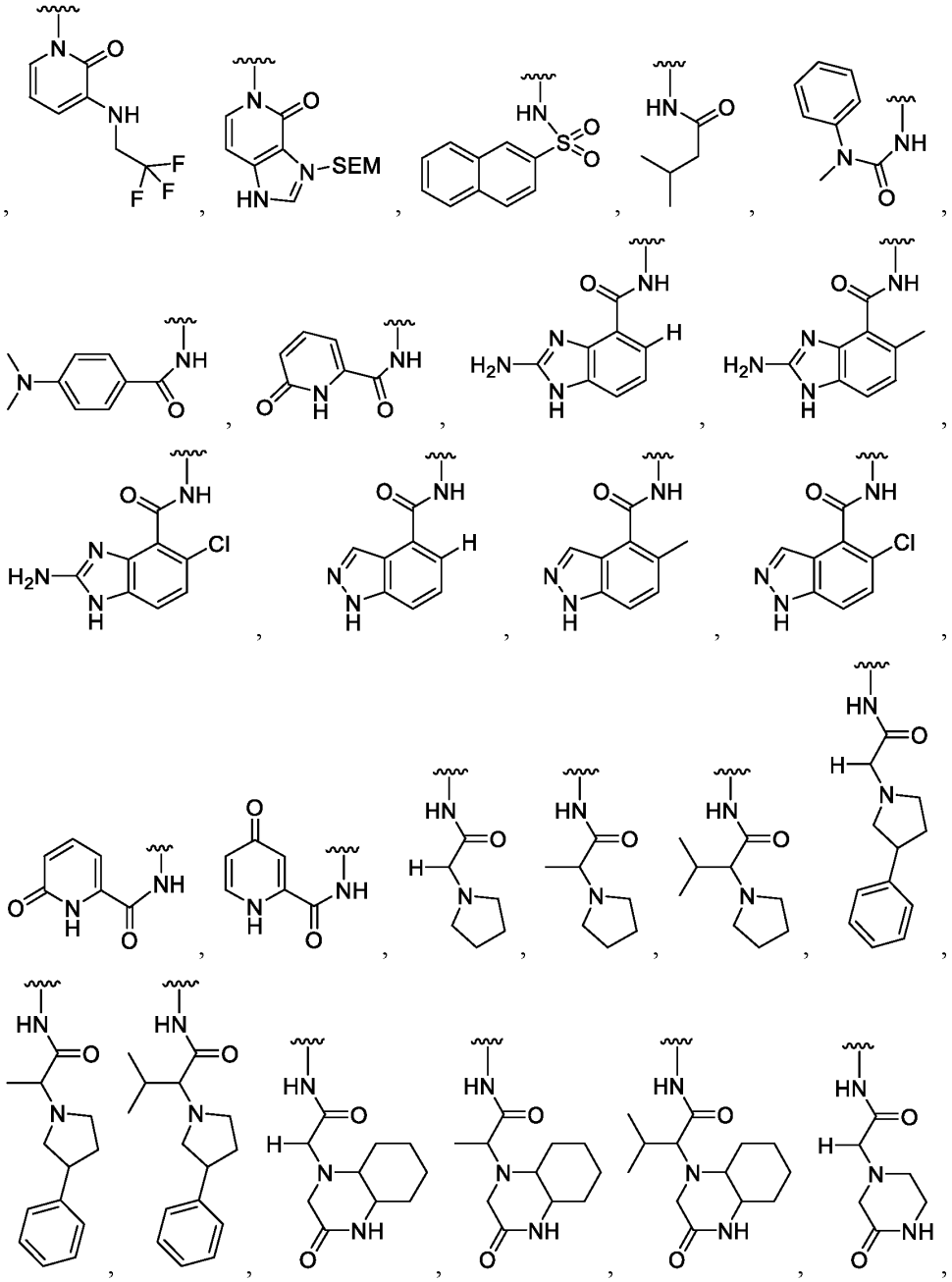


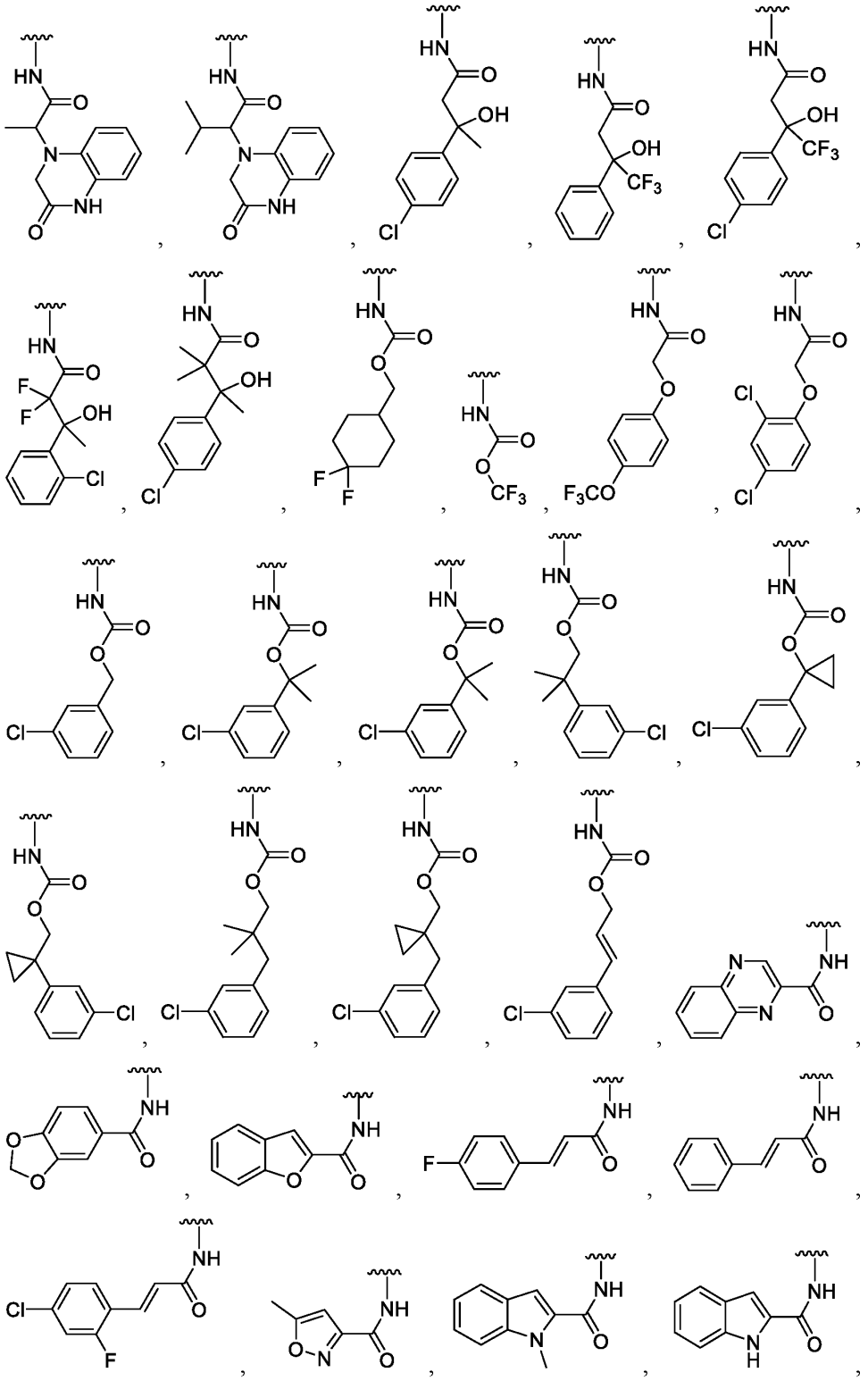


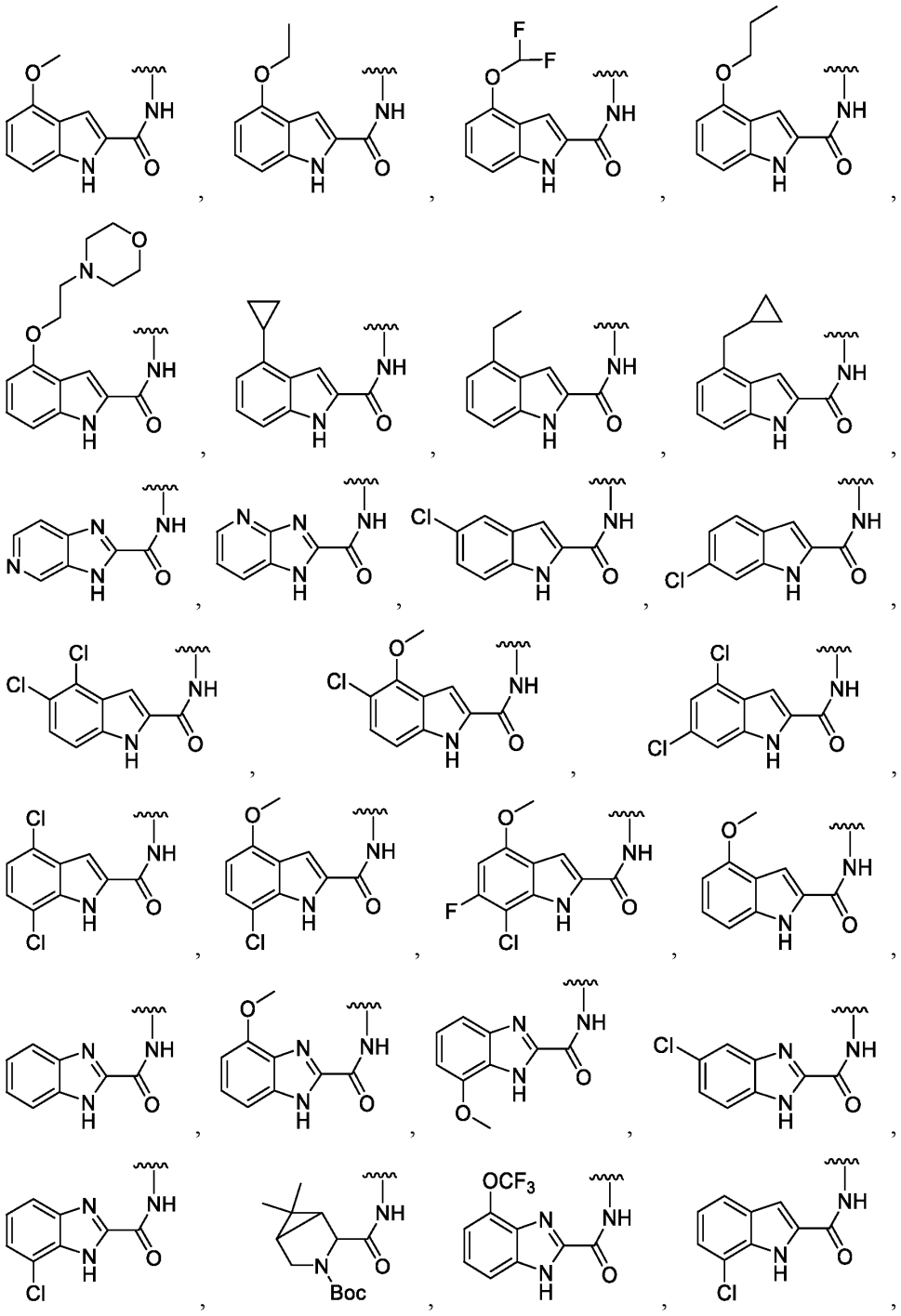
, and .

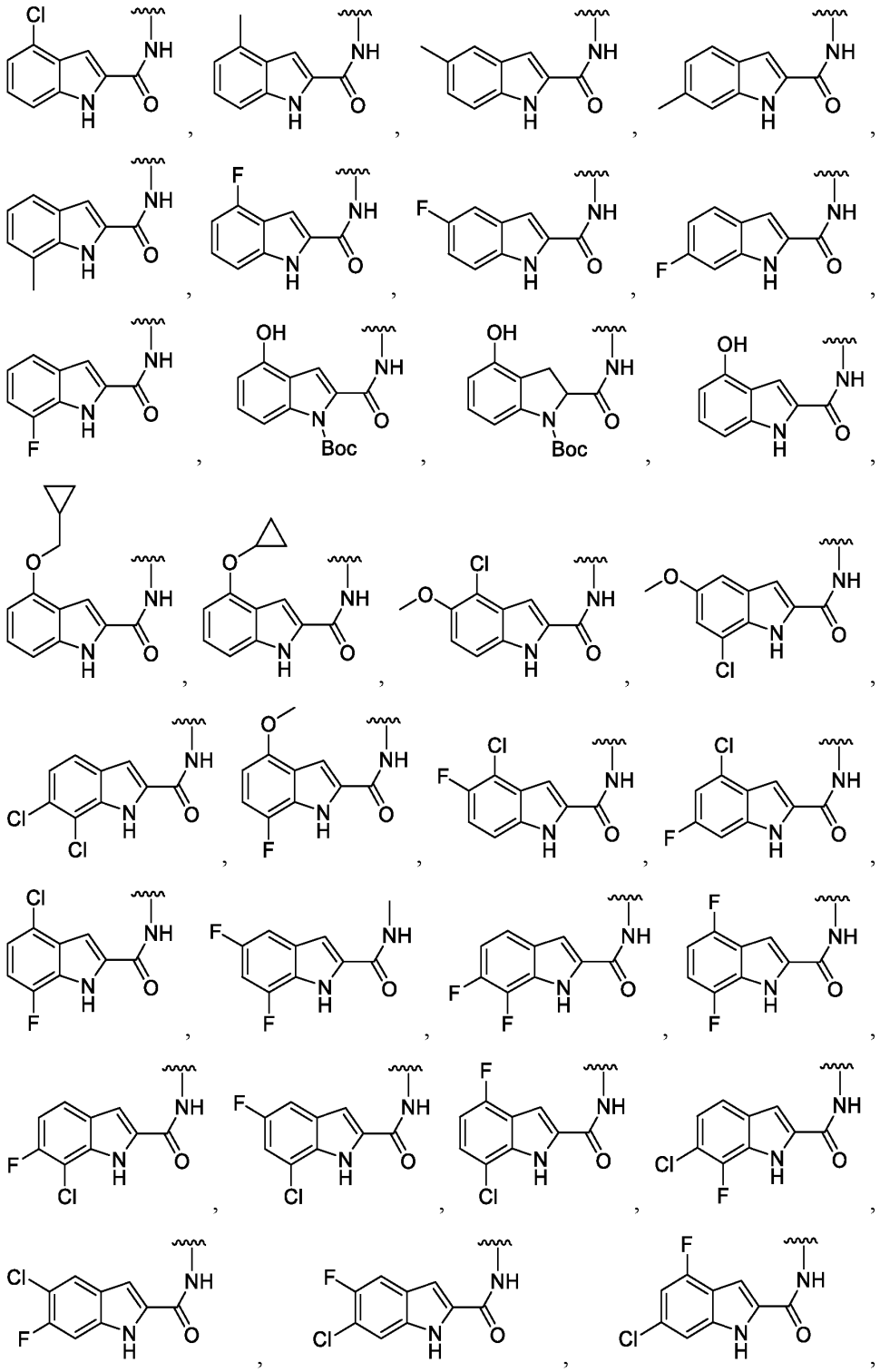
21. The compound of any one of claims 1-8, wherein R^2 is selected from the group consisting of

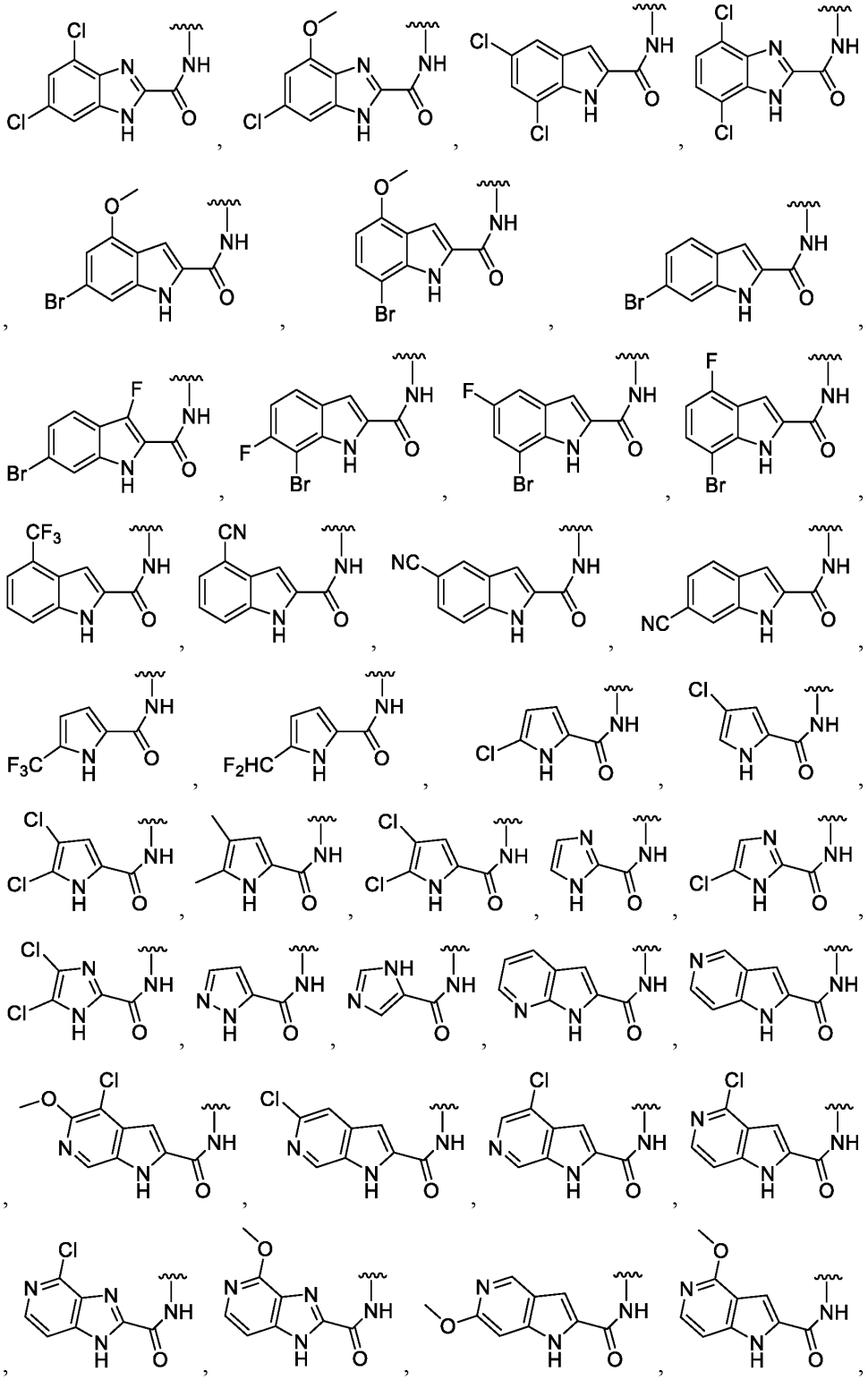


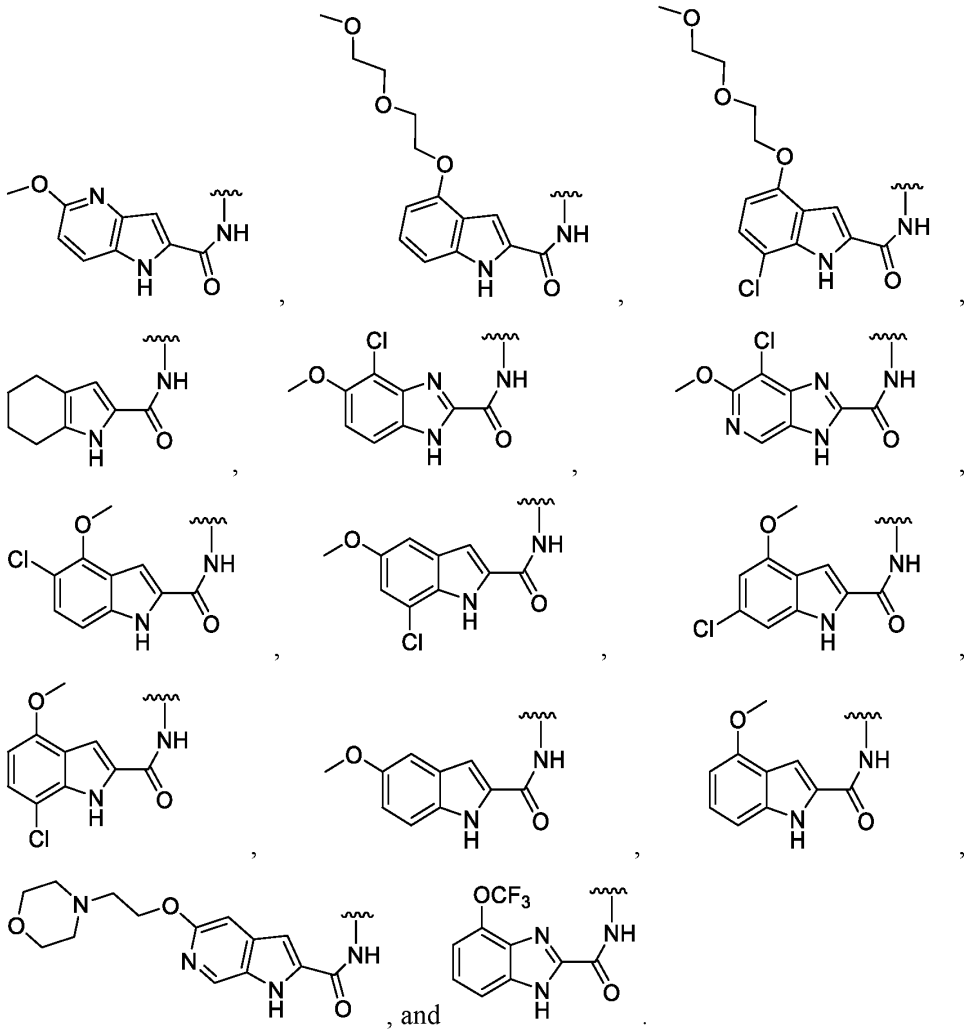




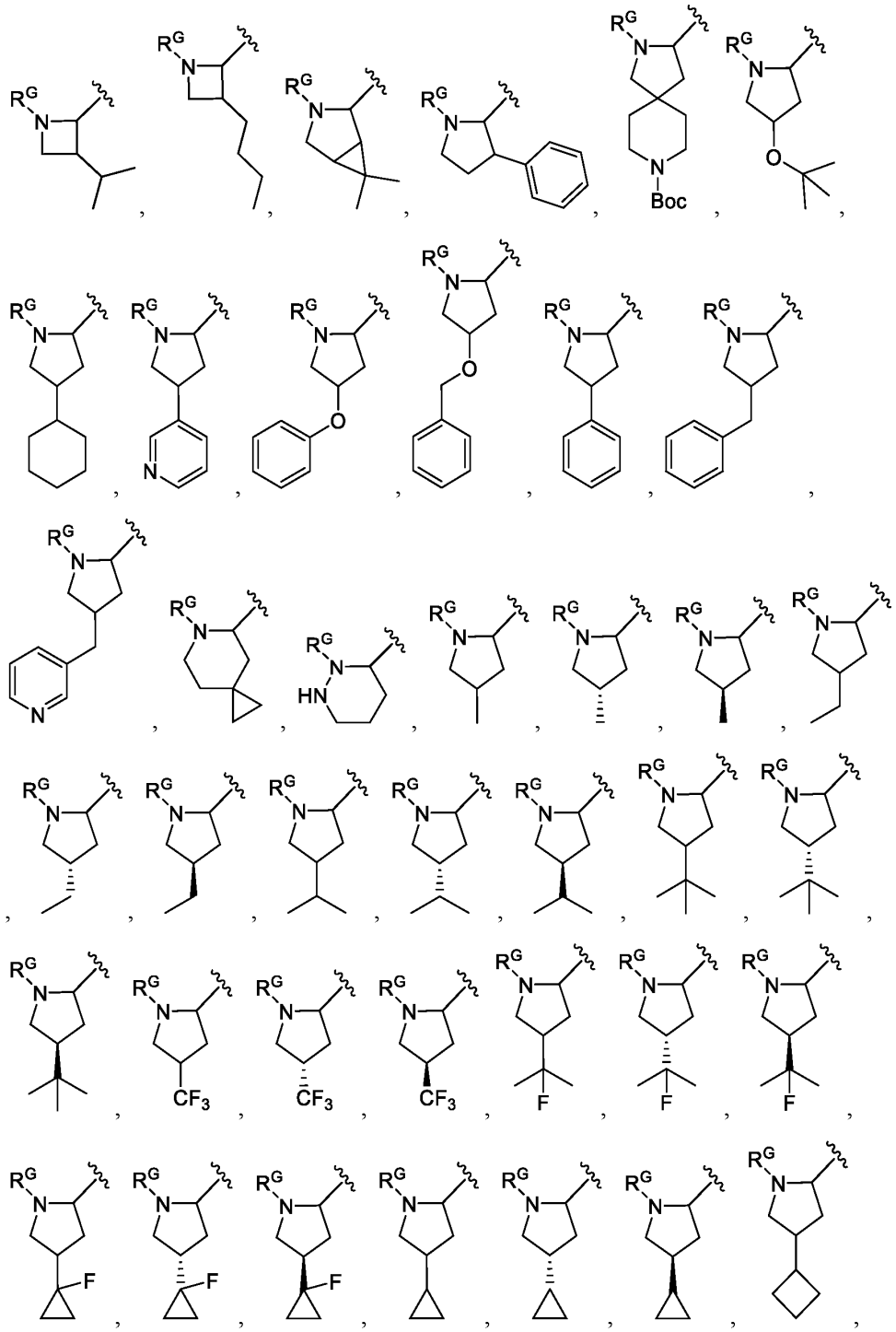


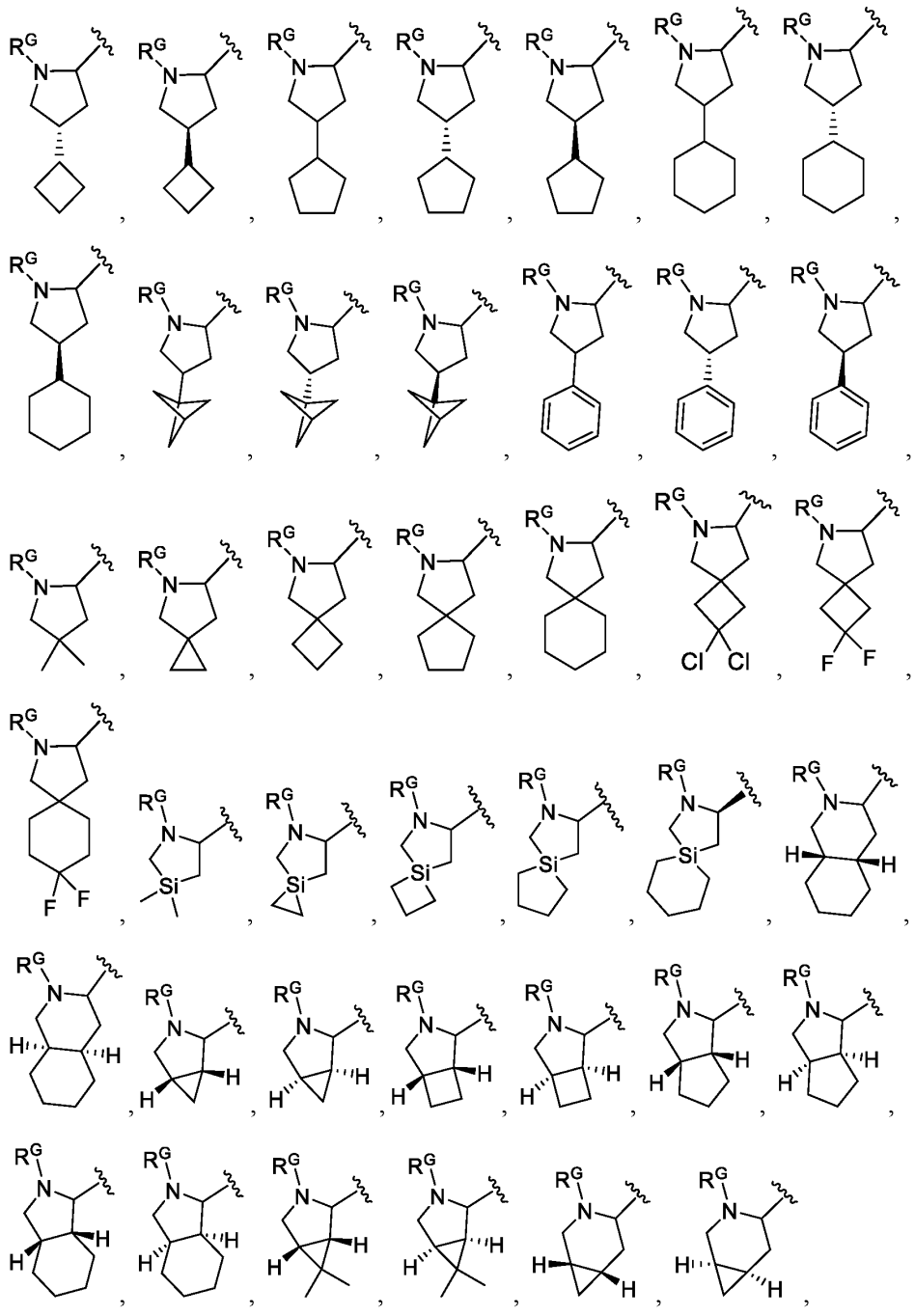


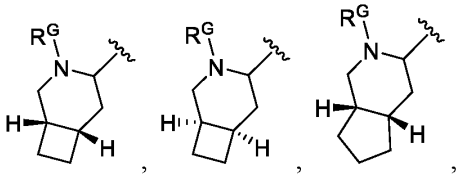


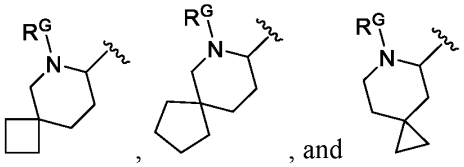


22. The compound of claim 1, wherein R^{1a} and R^2 are joined to together to form the heterocycle selected from the group consisting of:







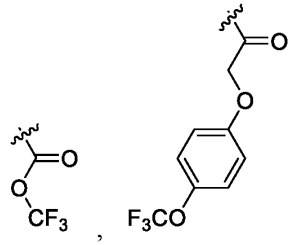


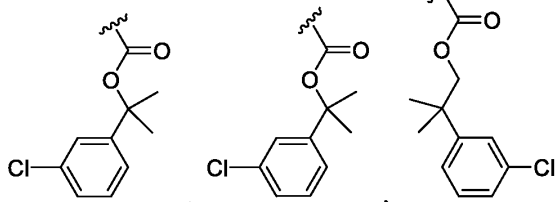
; wherein R^{1b} is H.

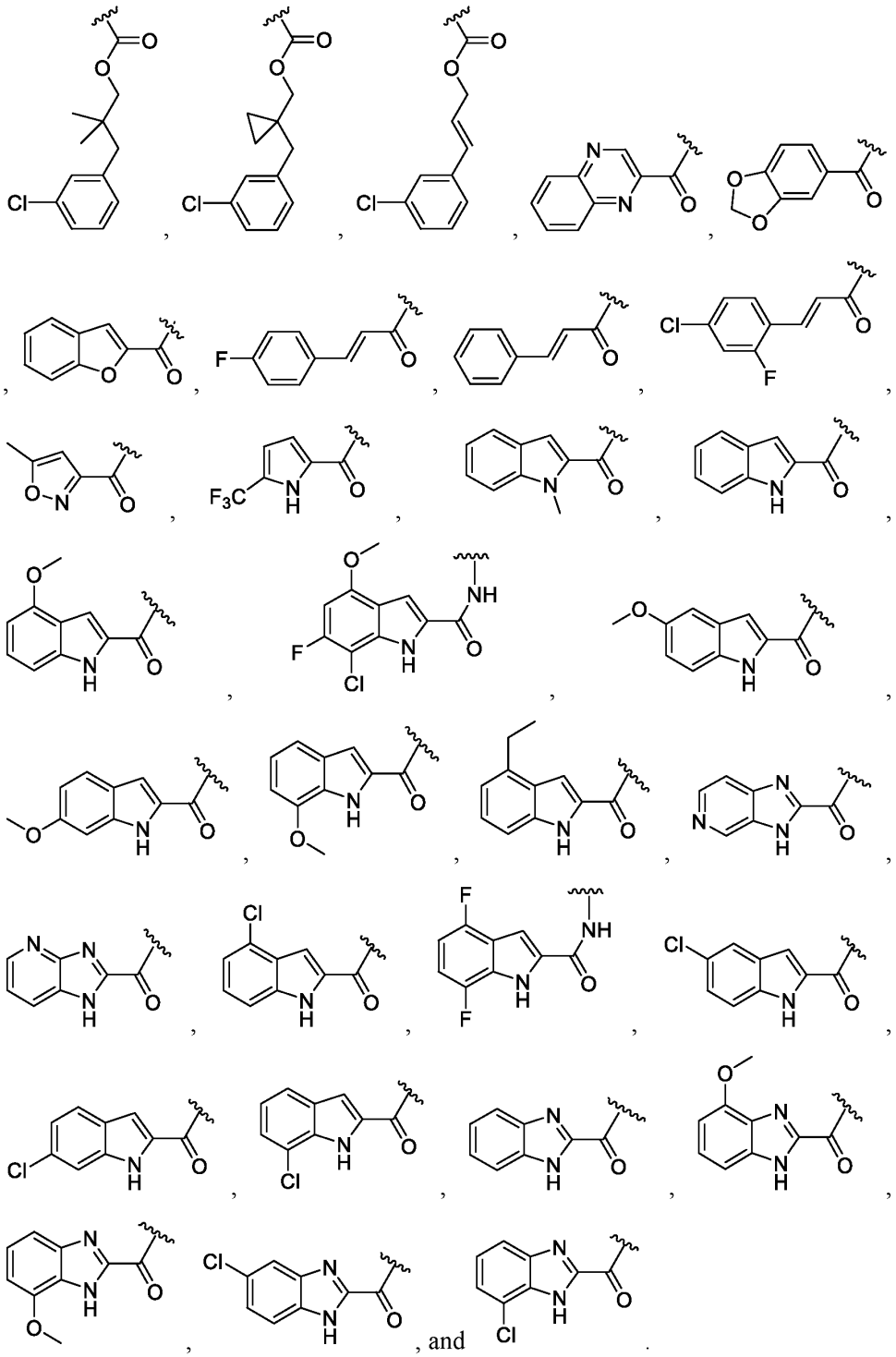
23. The compound of any one of claims 1, 10 and 22, wherein R^G is selected from the group consisting of hydrogen, C_{1-6}alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-C_{1-6}alkyl optionally substituted by one, two or three R^{hh}, and -C(=O)-C_{3-6}cycloalkyl.

24. The compound of any one of claims 1, 10 and 22, wherein R^G is selected from the group consisting of –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(4-10 membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{ii}.

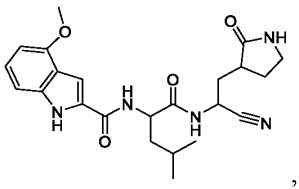
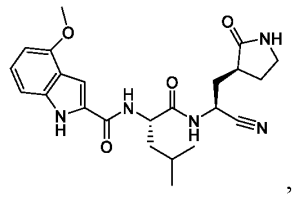
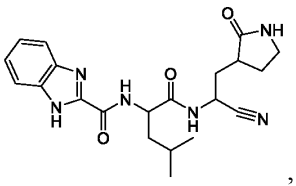
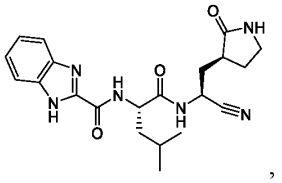
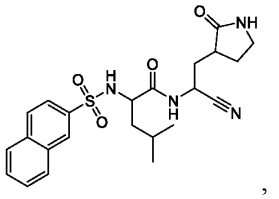
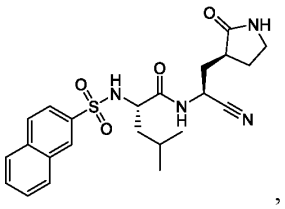
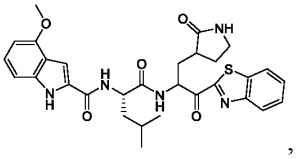
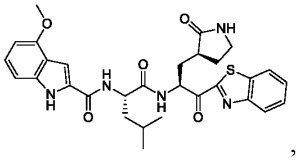
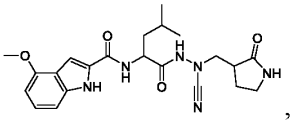
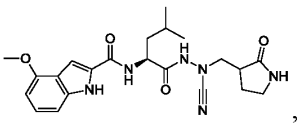
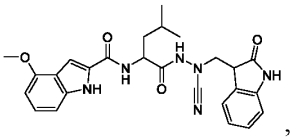
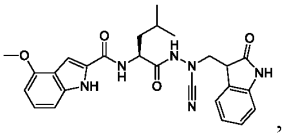
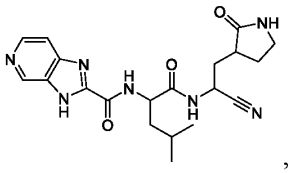
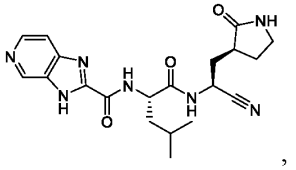
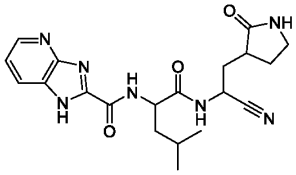
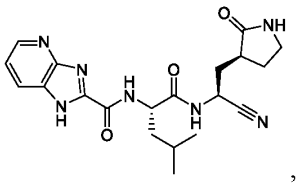
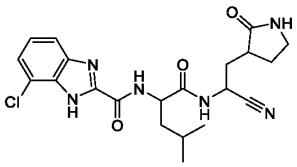
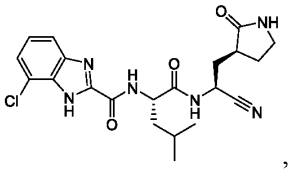
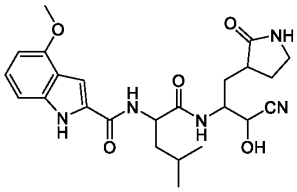
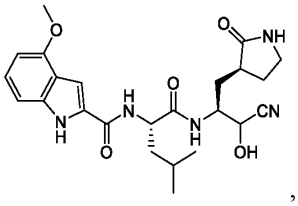
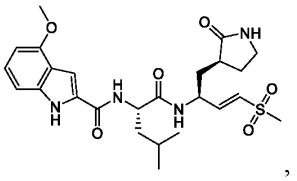
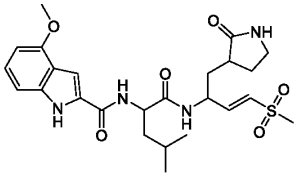
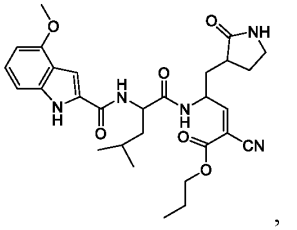
25. The compound of any one of claims 1, 10 and 22, wherein R^G is selected from the group consisting of

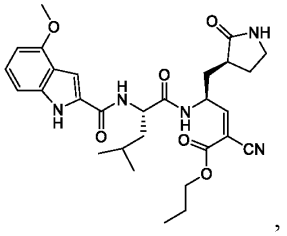
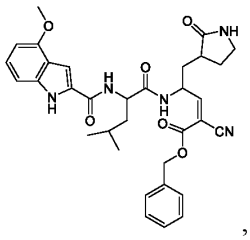
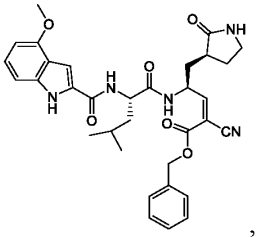
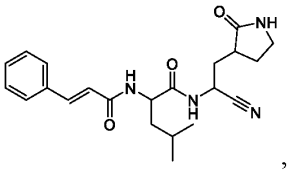
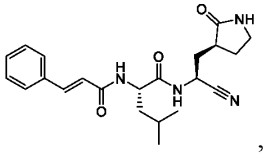
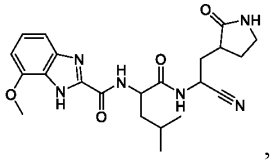
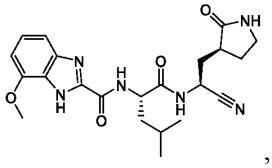
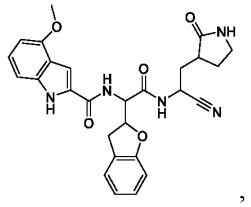
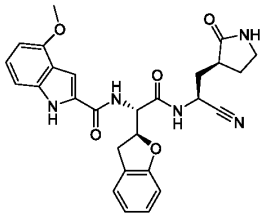
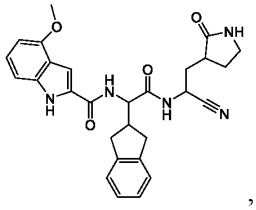
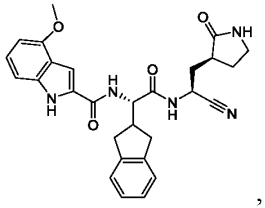
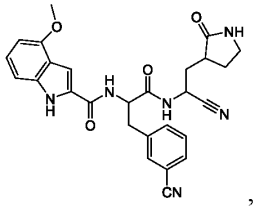
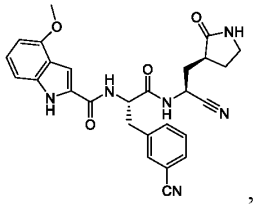
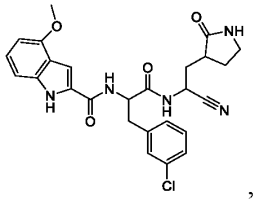
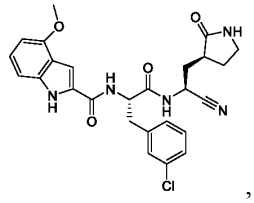
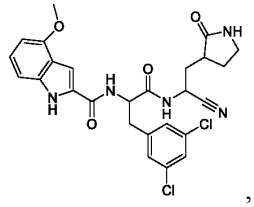
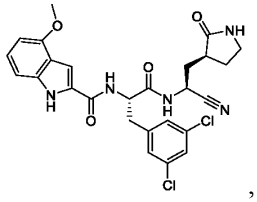
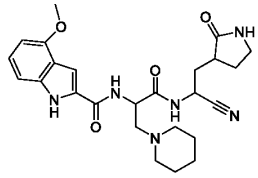
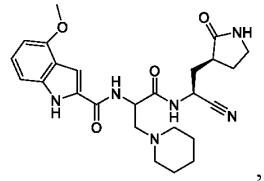
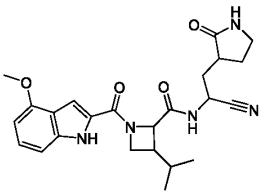


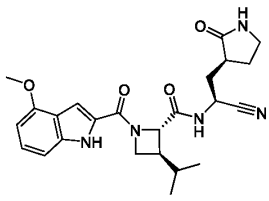


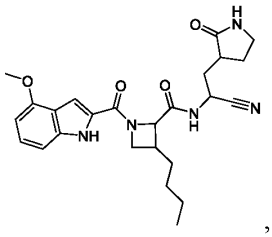
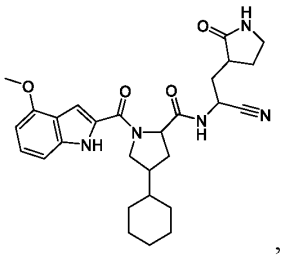
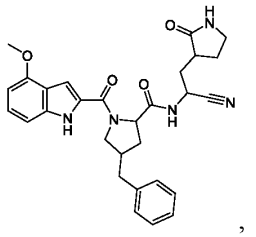
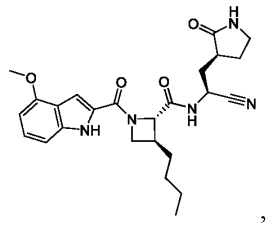
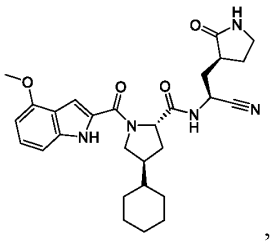
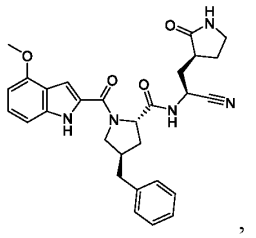
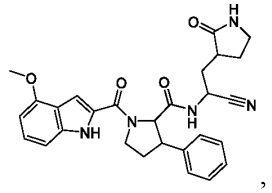
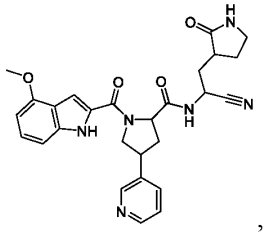
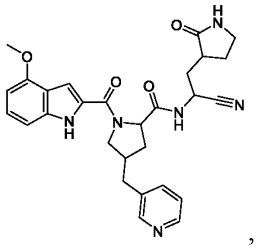
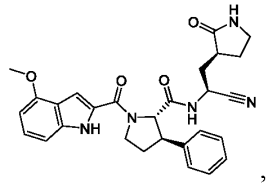
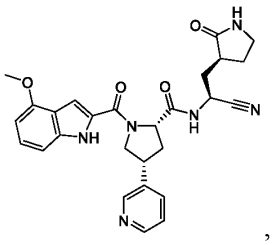
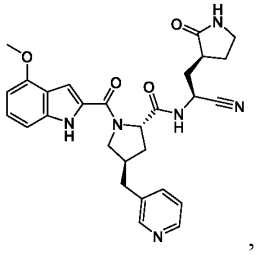
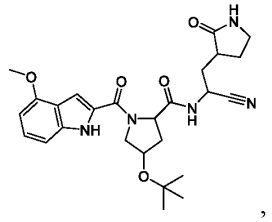
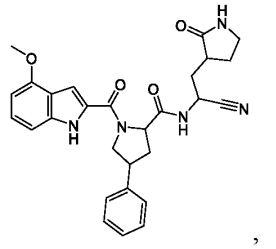
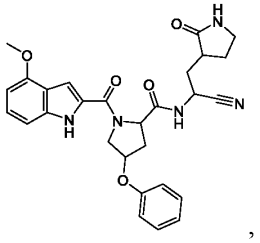
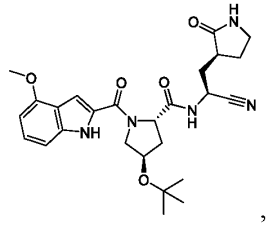


26. A compound selected from the group consisting of:


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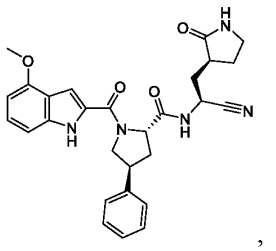
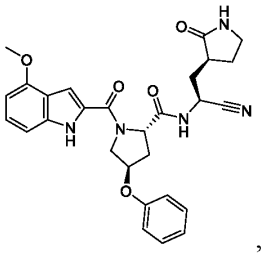

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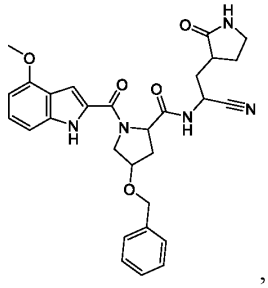
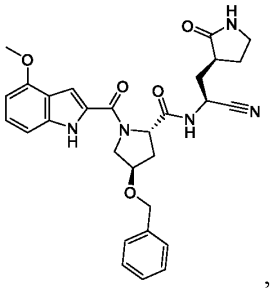
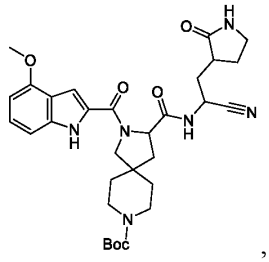
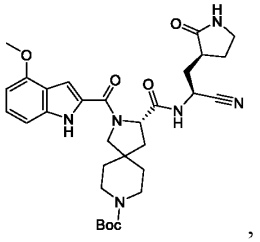
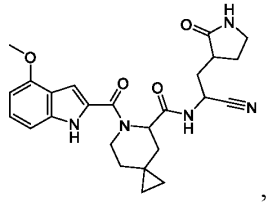
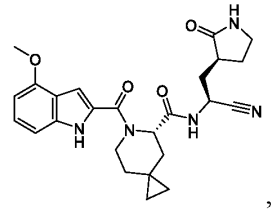
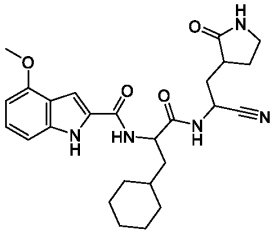
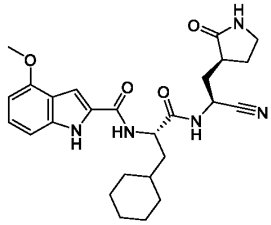
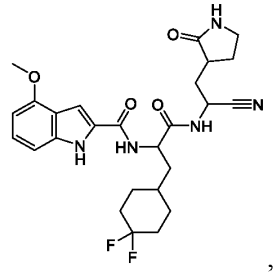
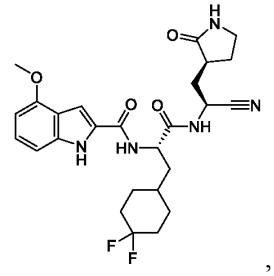
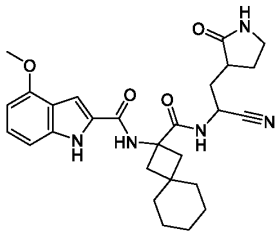
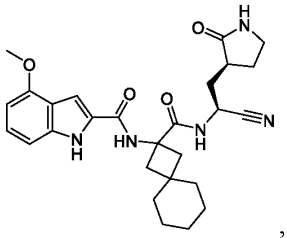
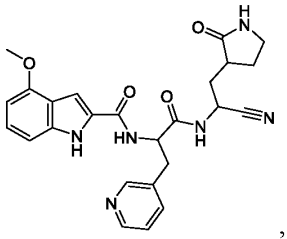
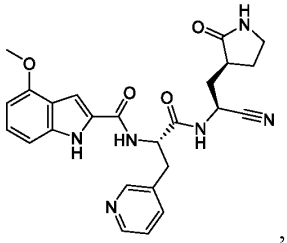
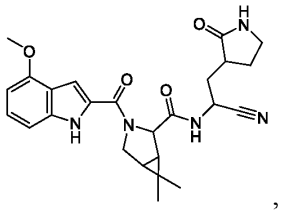
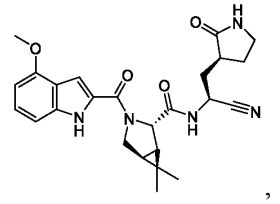
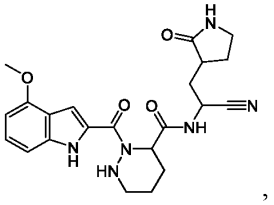
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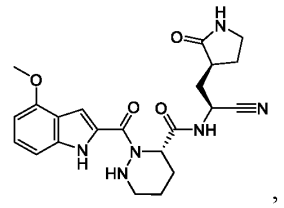
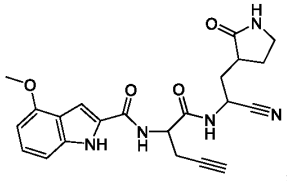
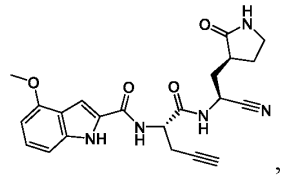
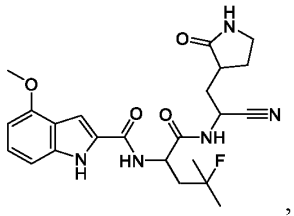
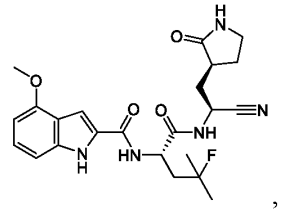
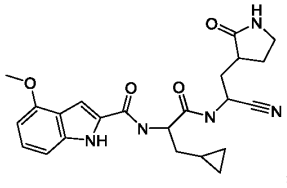
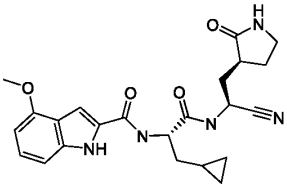
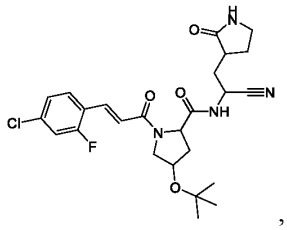
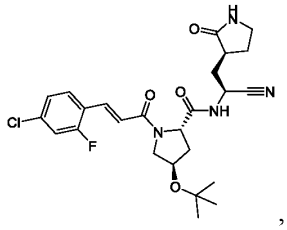
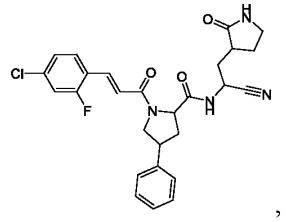
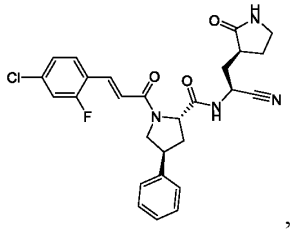
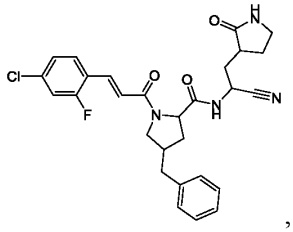
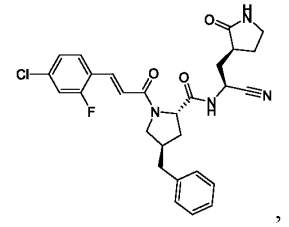
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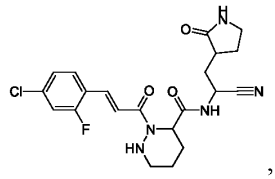
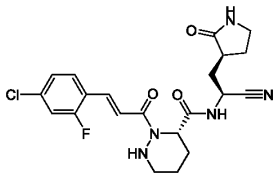
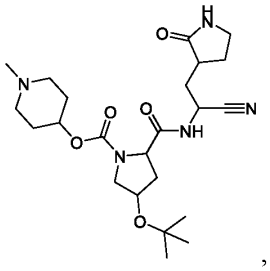
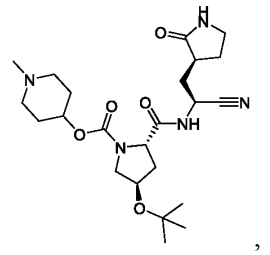
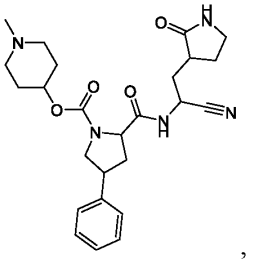
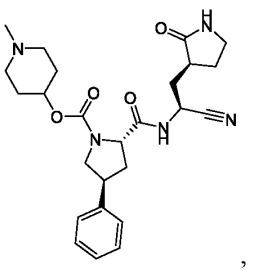
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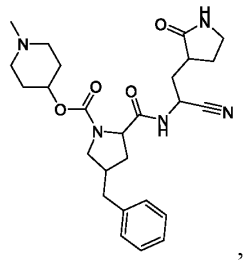
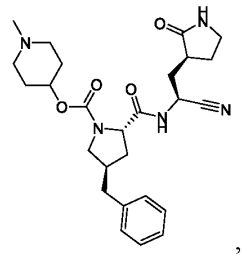
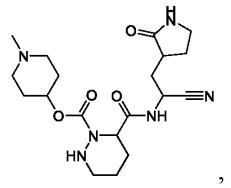
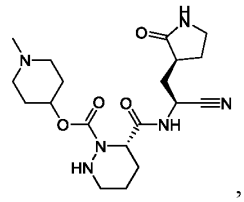
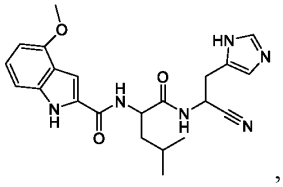
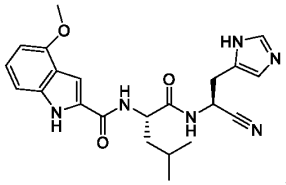
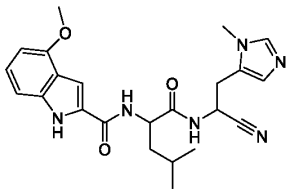
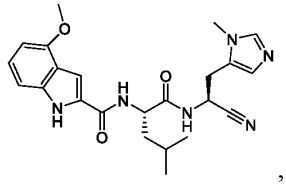
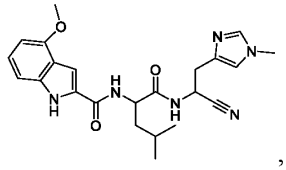
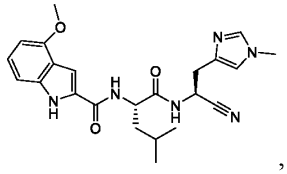
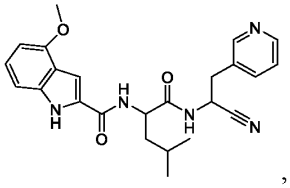
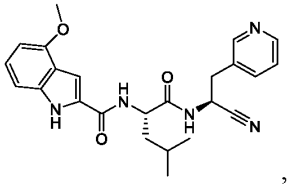
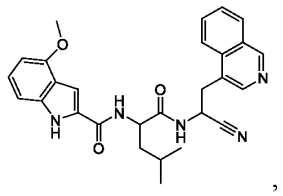
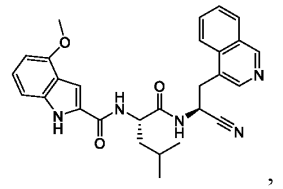
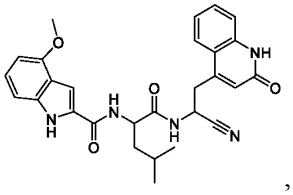
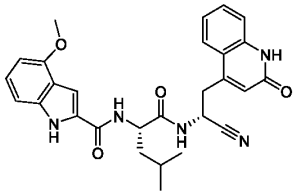
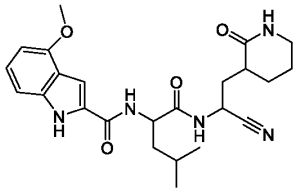
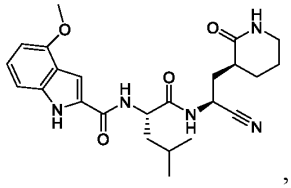
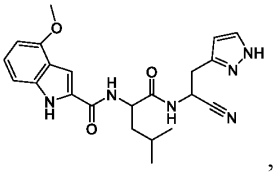
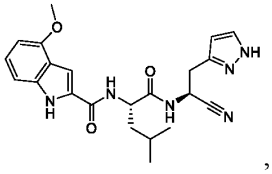
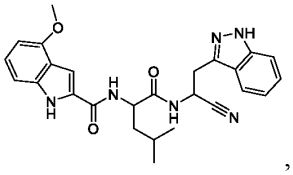
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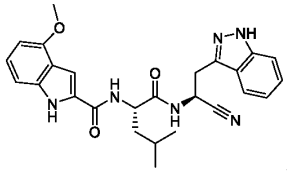
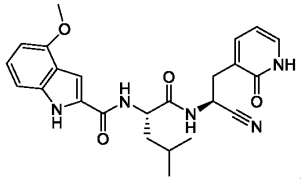
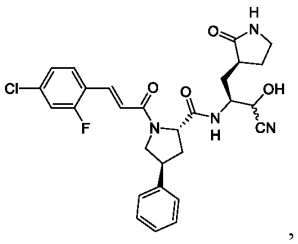
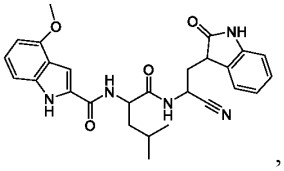
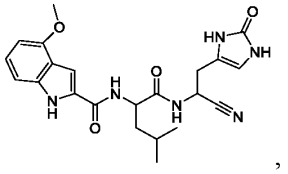
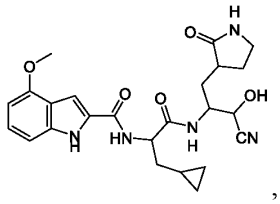
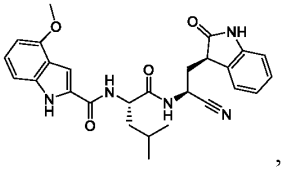
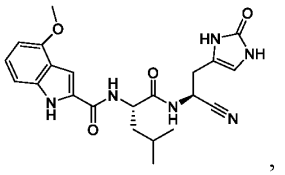
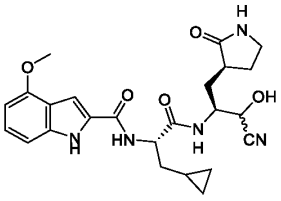
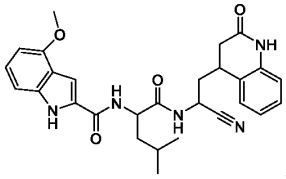
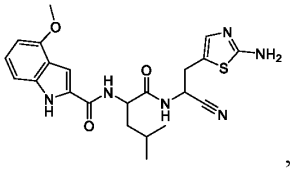
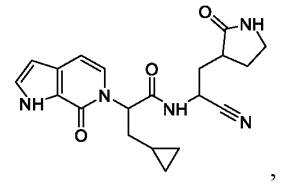
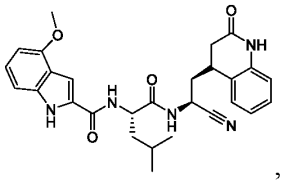
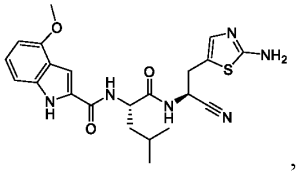
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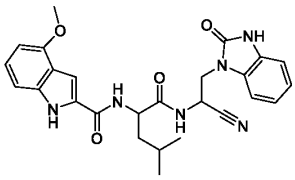
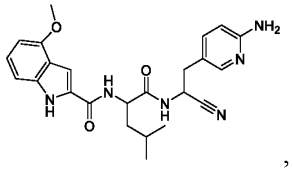
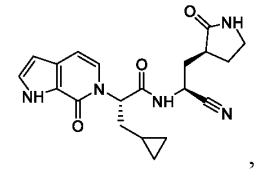
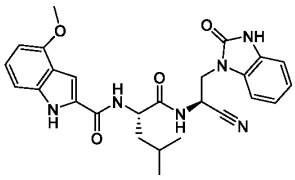
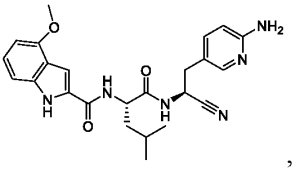
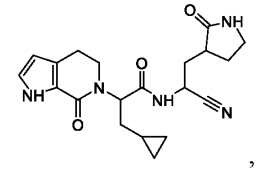
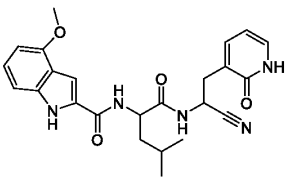
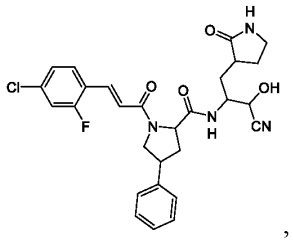
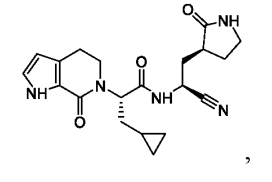

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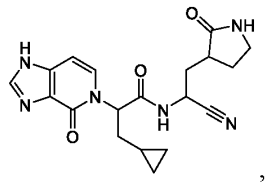
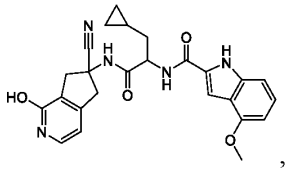
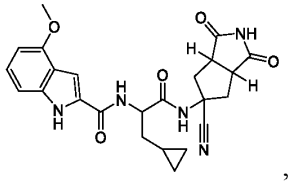
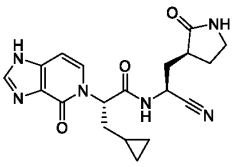
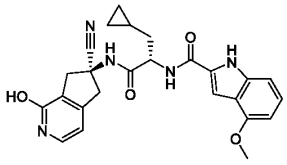
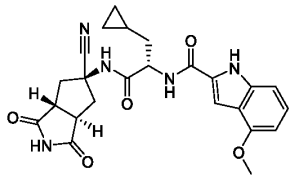
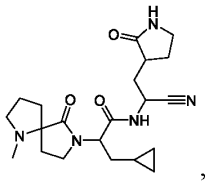
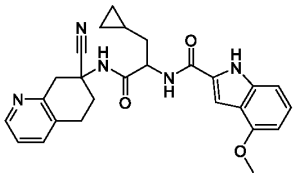
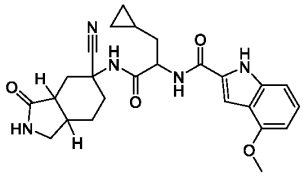
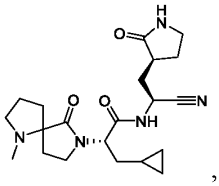
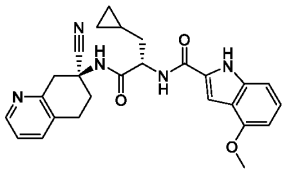
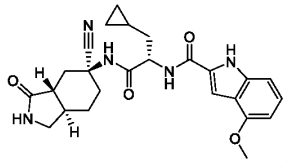
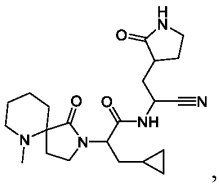
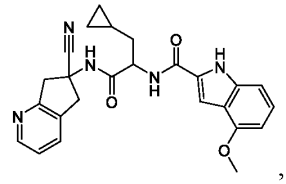
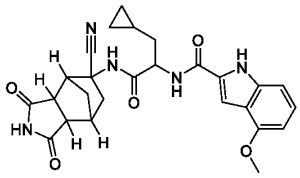
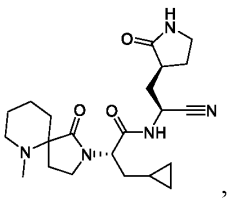
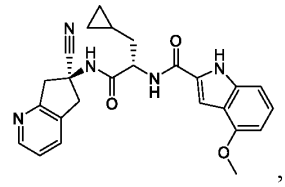
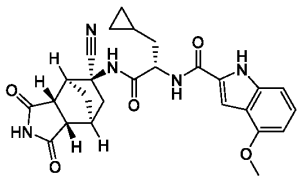
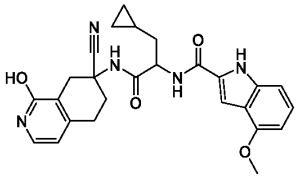
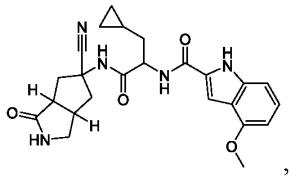
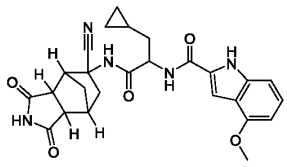
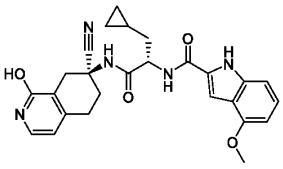
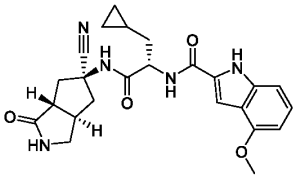
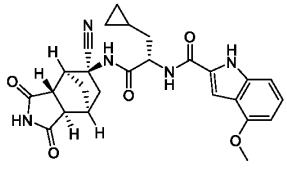

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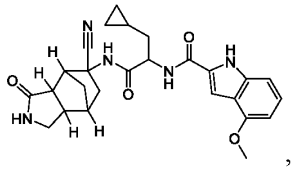
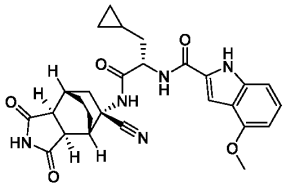
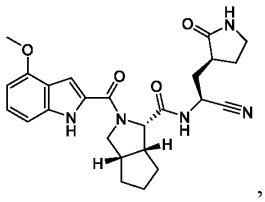
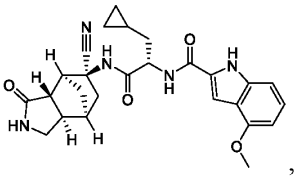
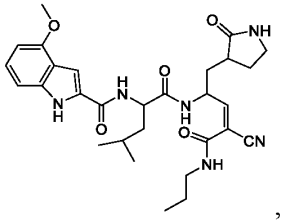
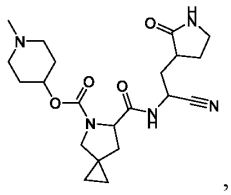
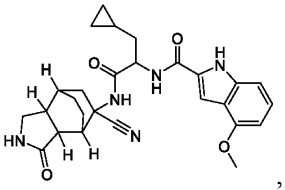
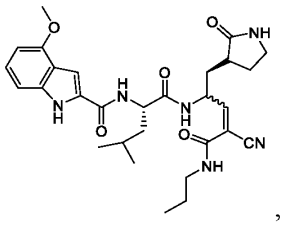
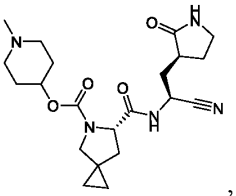
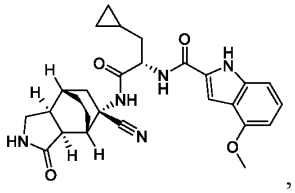
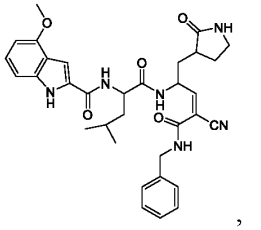
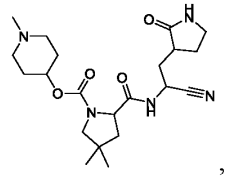
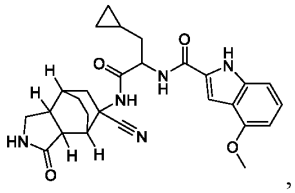
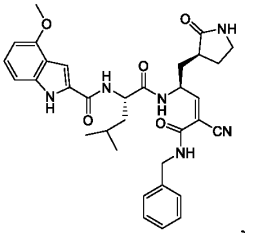
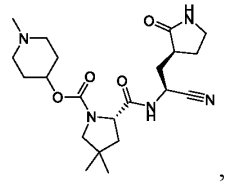
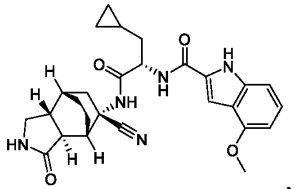
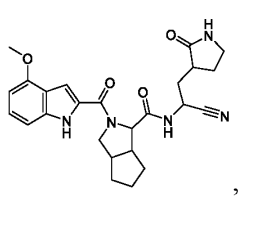
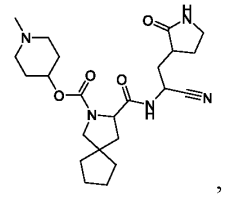
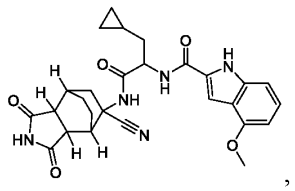
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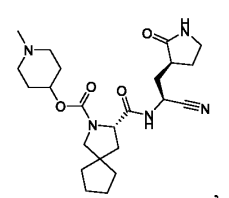

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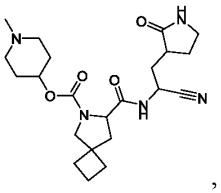
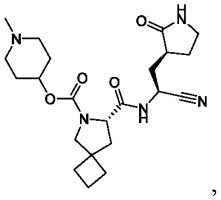
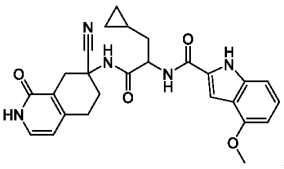
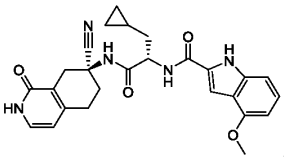
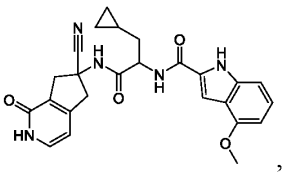
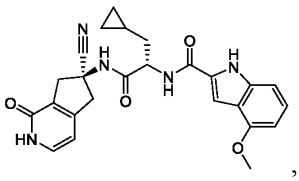
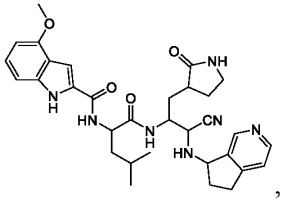
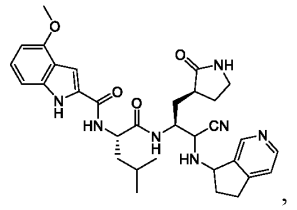
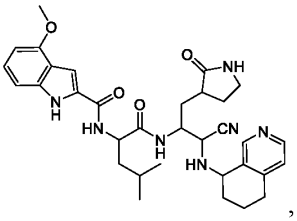
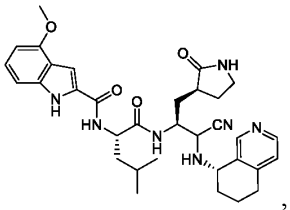
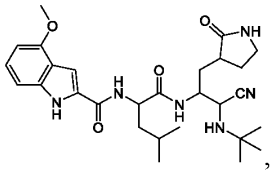
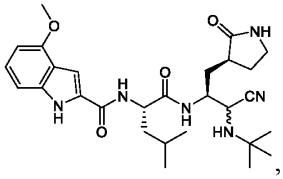
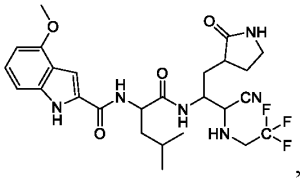
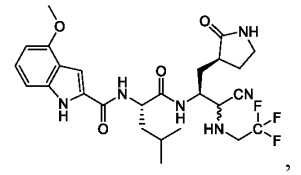

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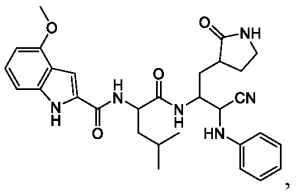
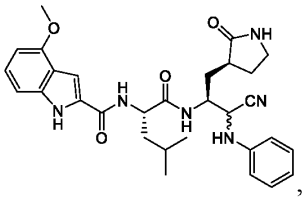
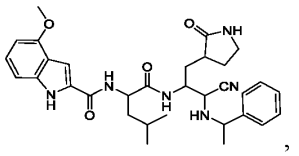
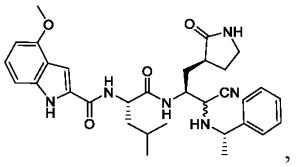
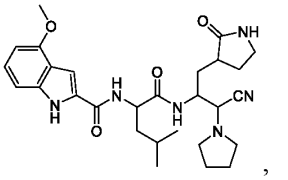
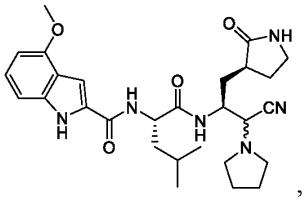
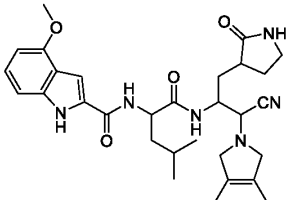

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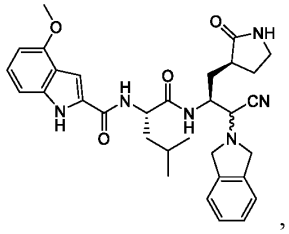
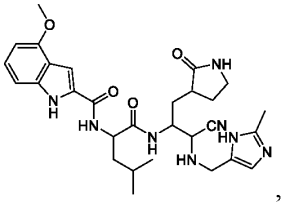
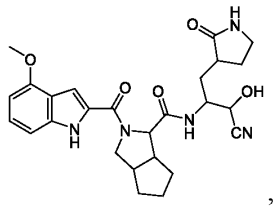
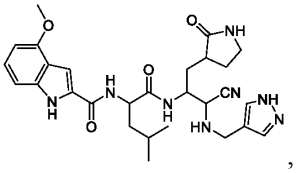
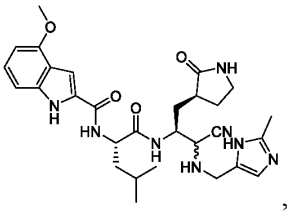
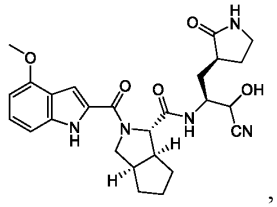
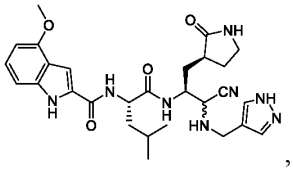
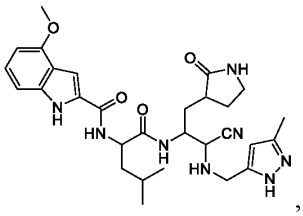
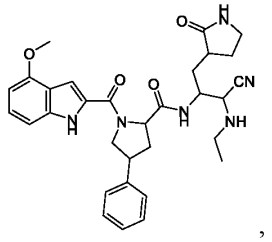
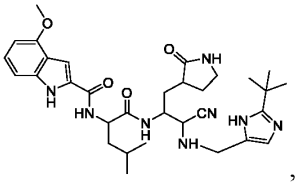
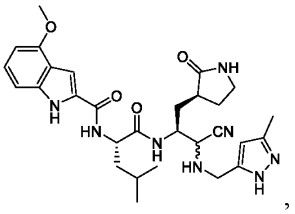
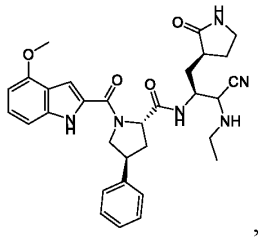
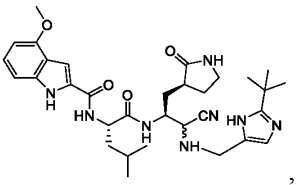
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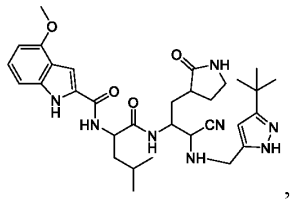
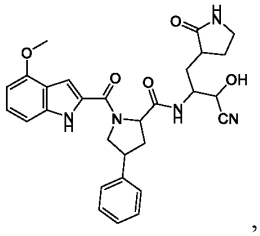
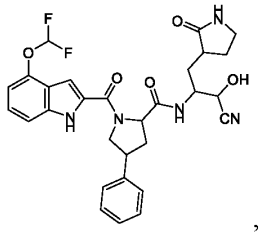
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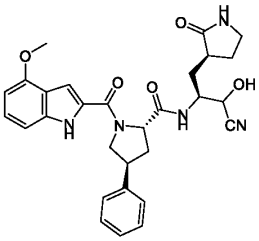

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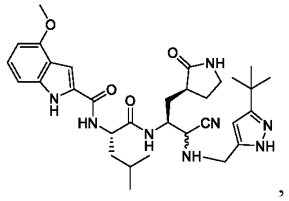
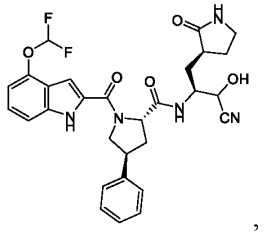
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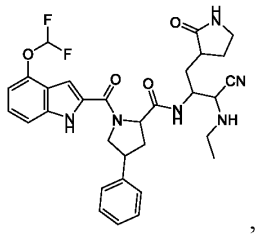
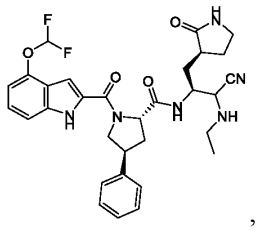
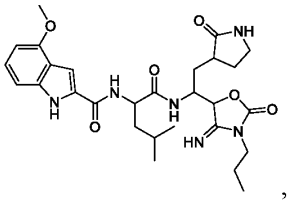
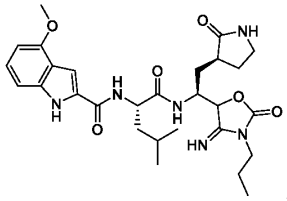
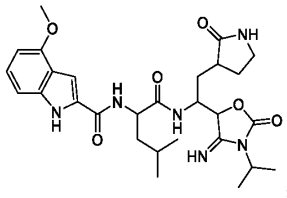
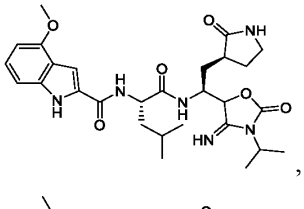
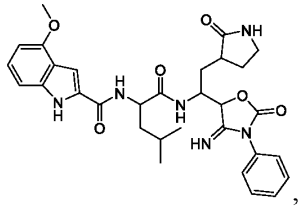
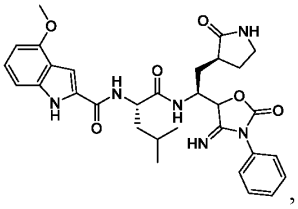
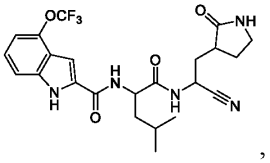
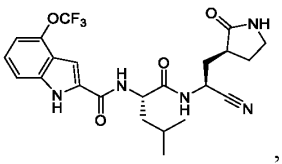
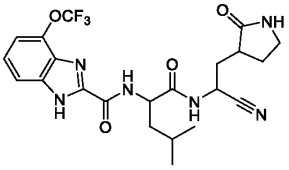
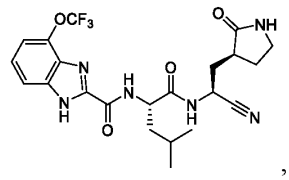
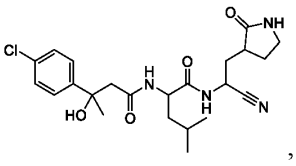
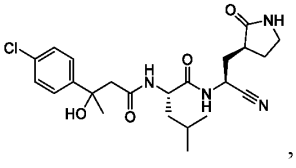
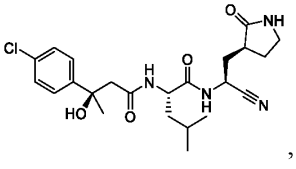
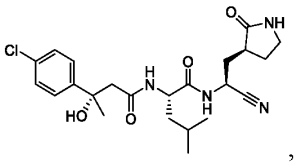
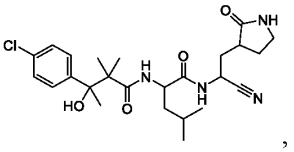
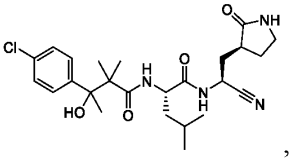
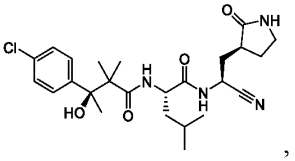
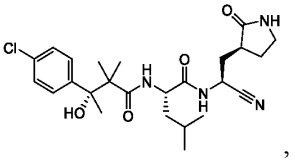
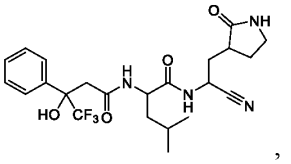
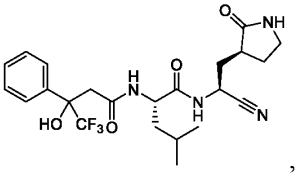
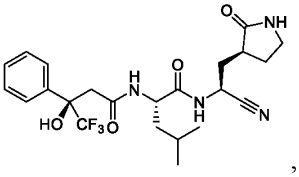

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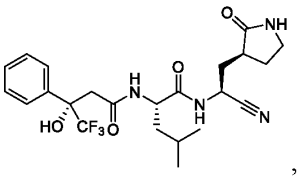
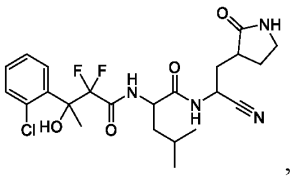
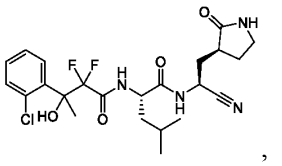
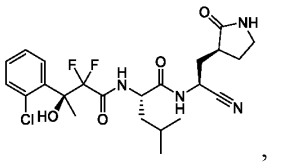
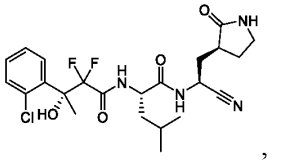
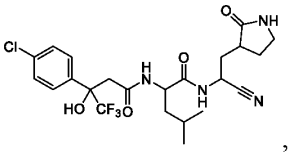
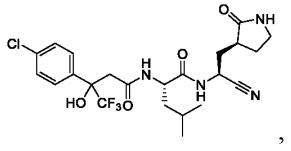
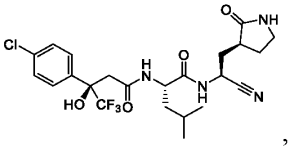
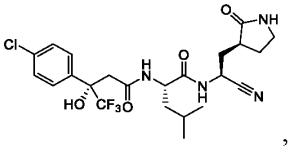
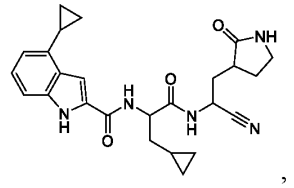
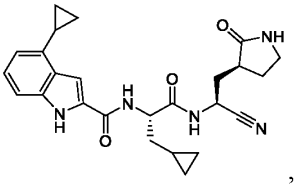
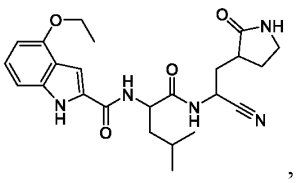
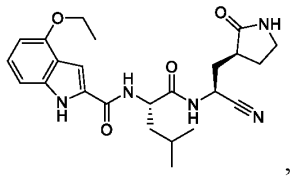
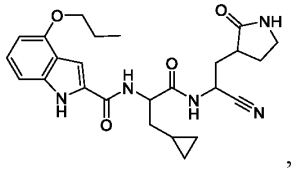
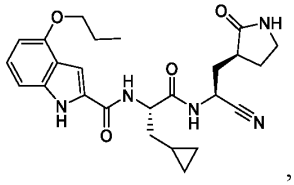
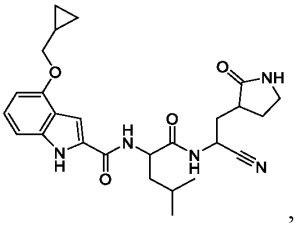
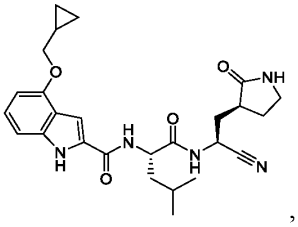
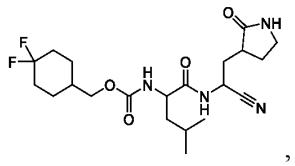
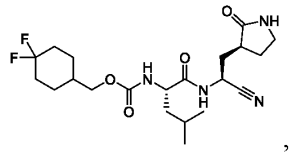
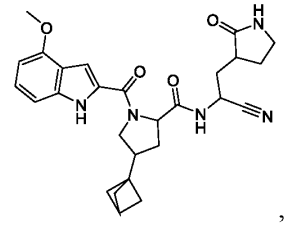
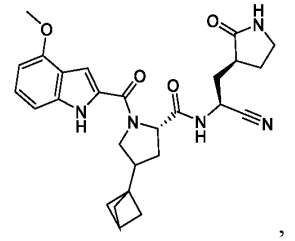
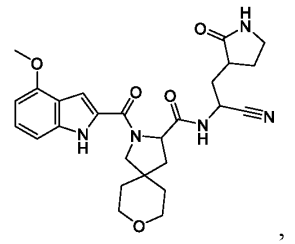
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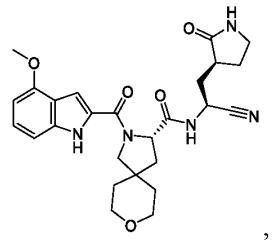
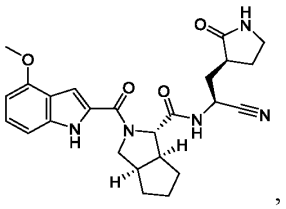
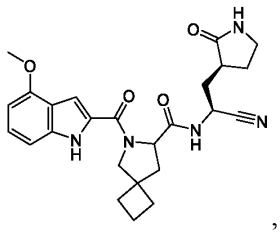
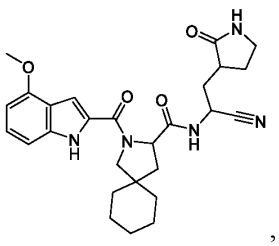
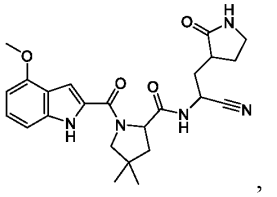
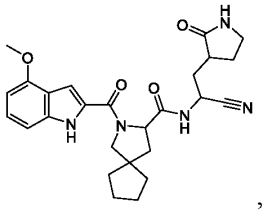
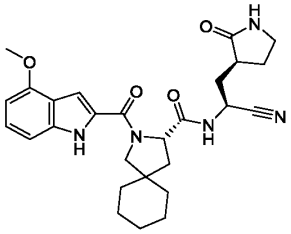
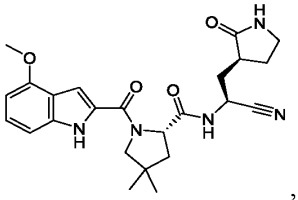
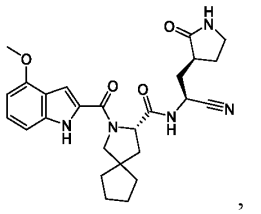
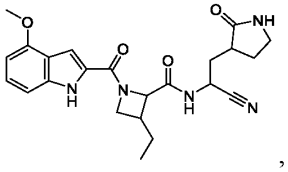
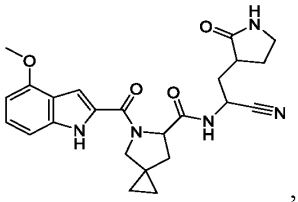
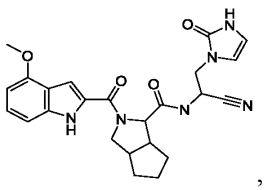
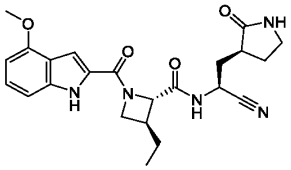
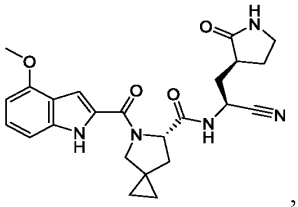
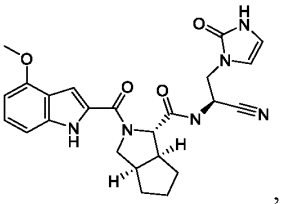
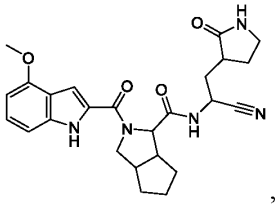
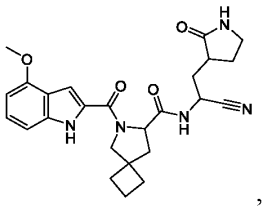
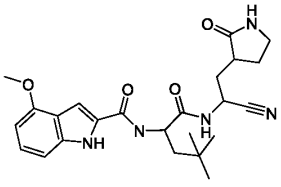
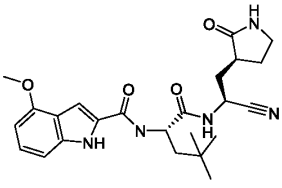
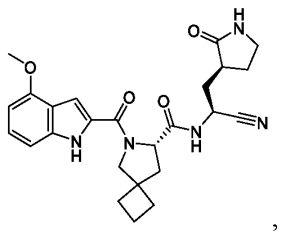
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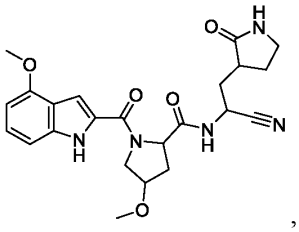
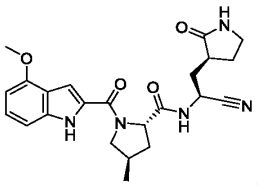
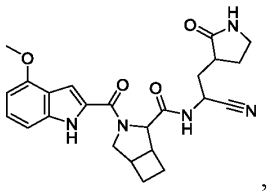
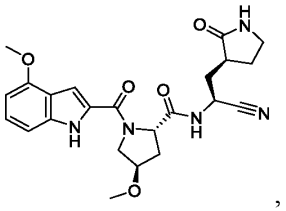
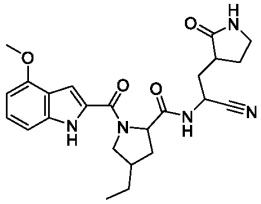
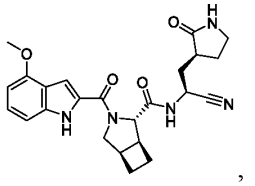
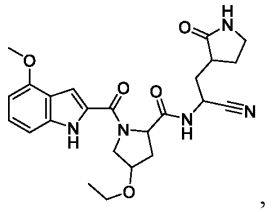
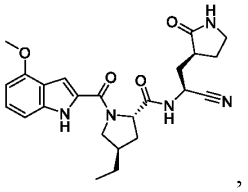
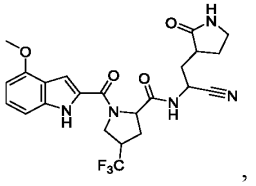
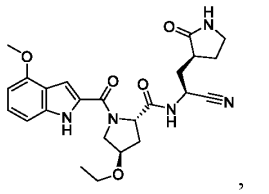
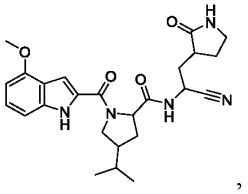
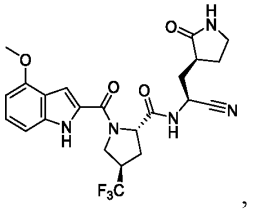
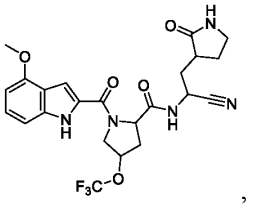
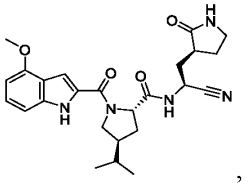
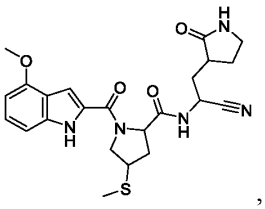
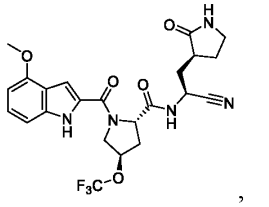
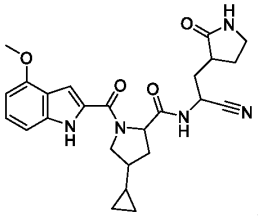
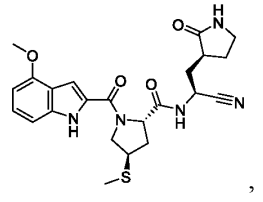
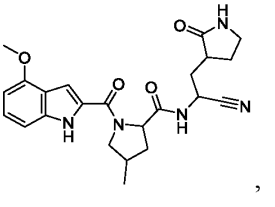
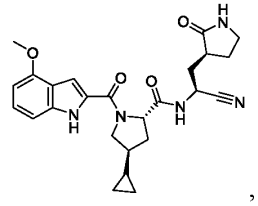
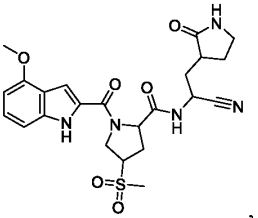

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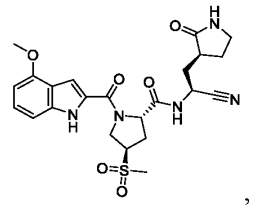
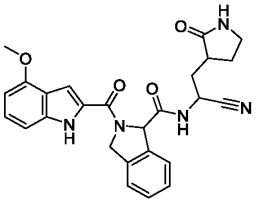
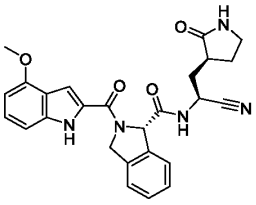
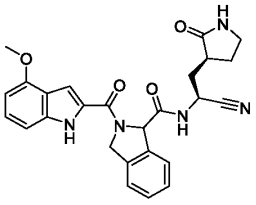
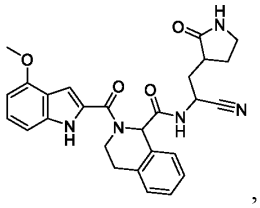
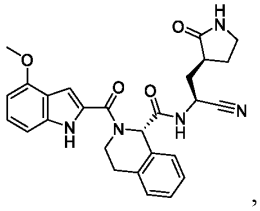
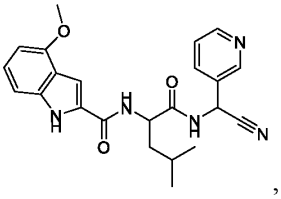
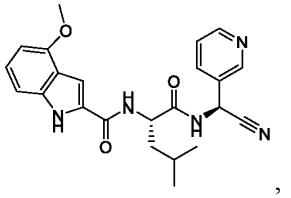
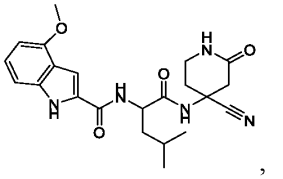
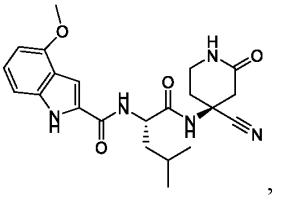
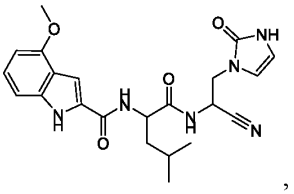
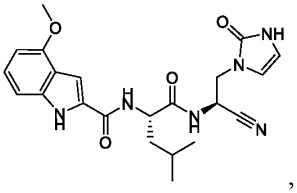
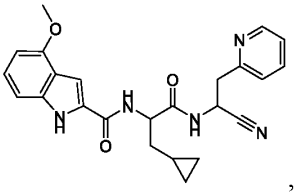
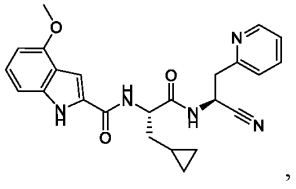
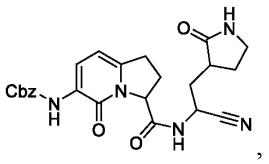
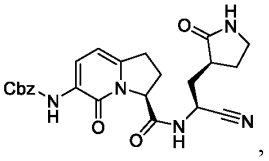
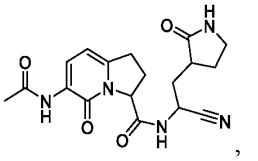
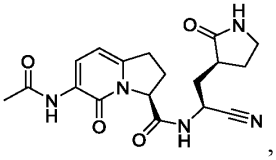
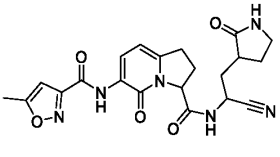
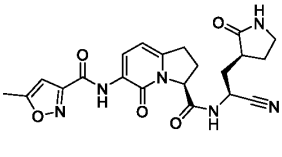
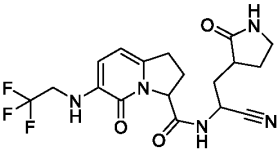
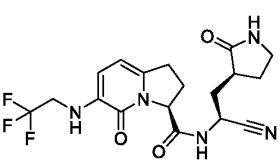
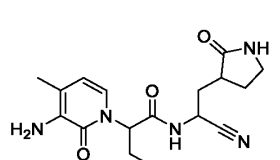
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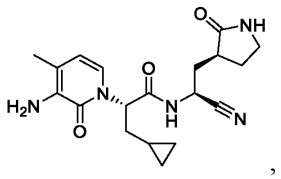
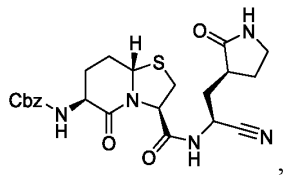
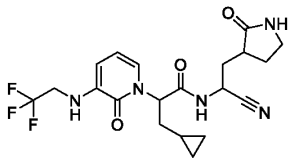
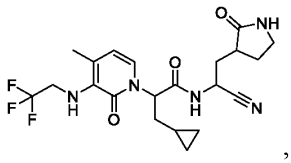
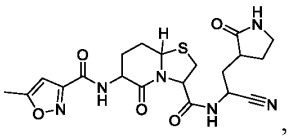
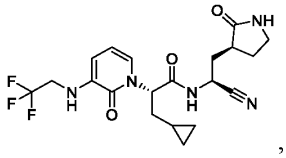
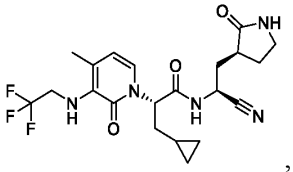
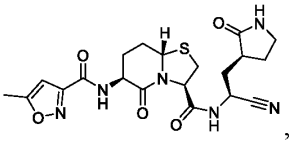
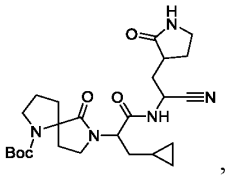
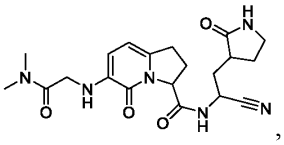
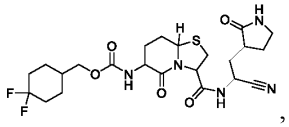
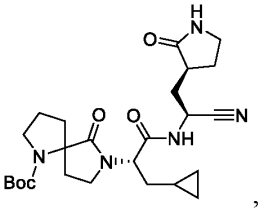
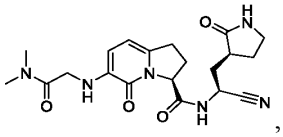
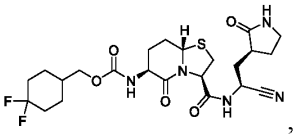
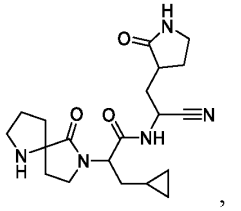
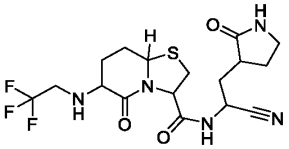
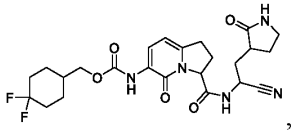
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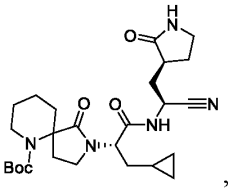
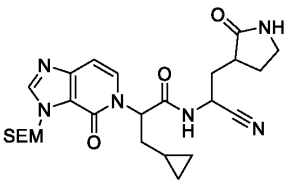
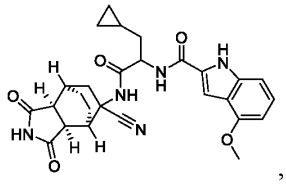
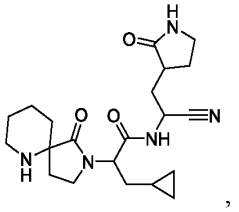
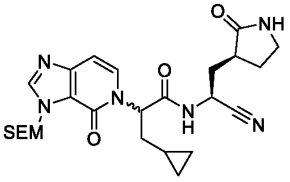
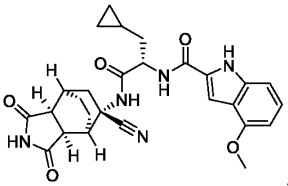
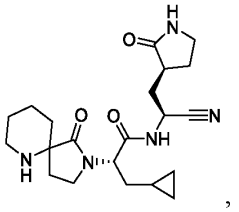
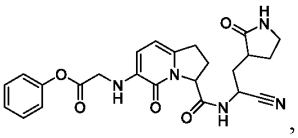
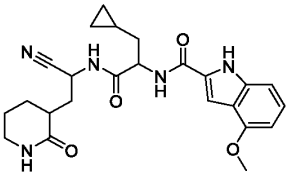
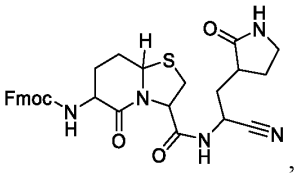
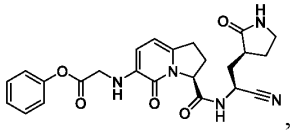
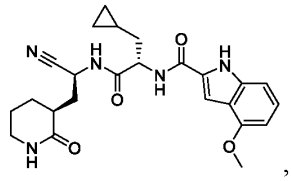
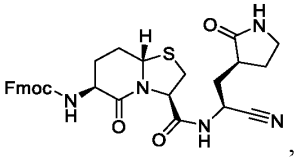
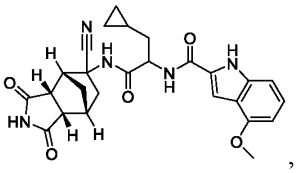
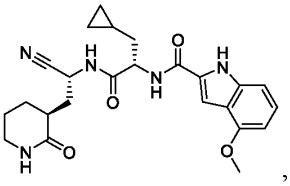
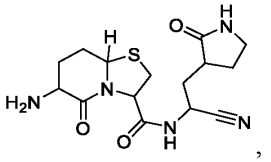
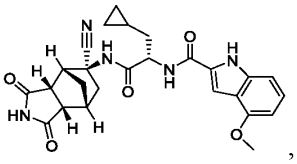
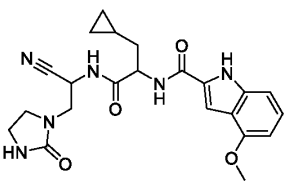
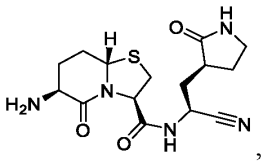
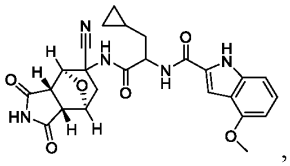
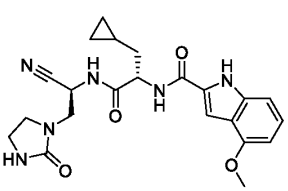
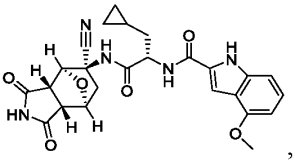
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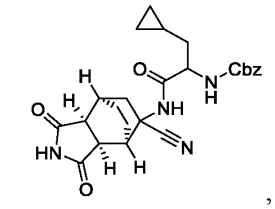
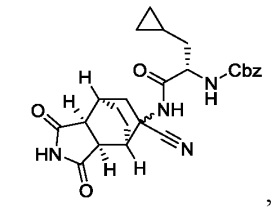
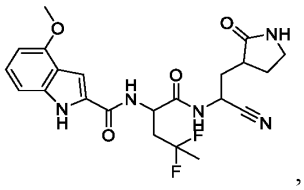
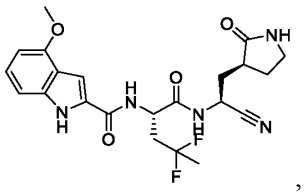
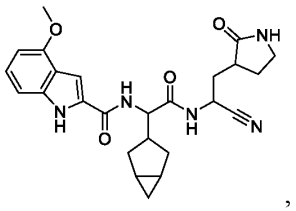
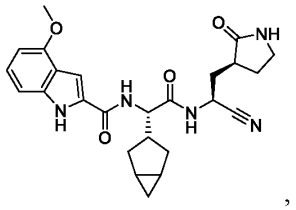
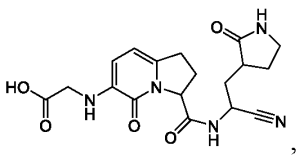
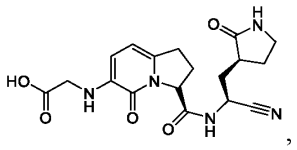
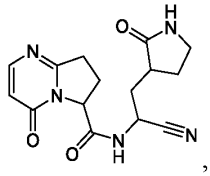
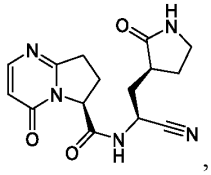
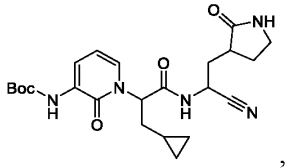
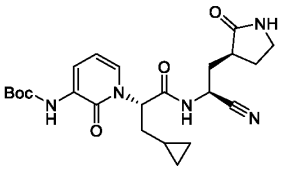
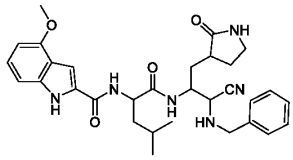
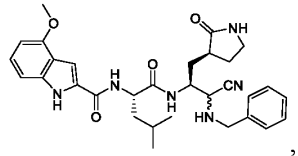
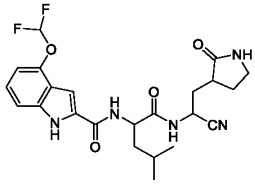
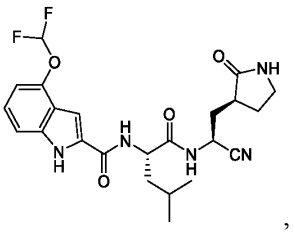
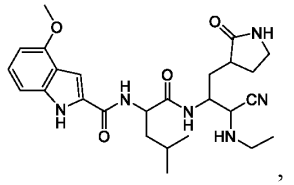
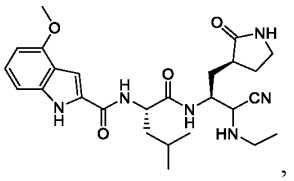
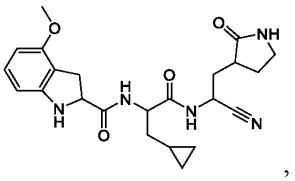
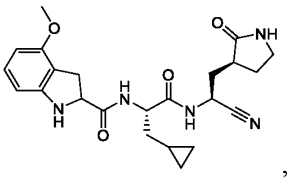
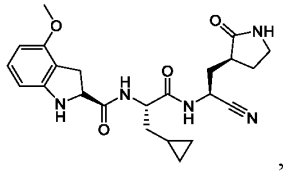
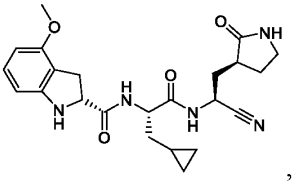
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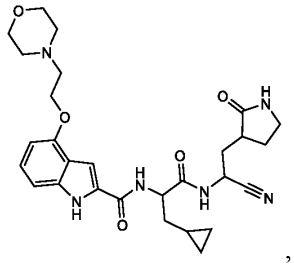
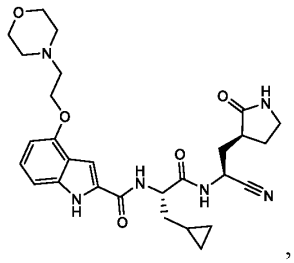
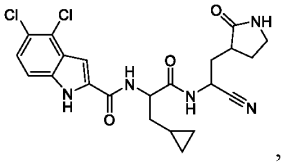
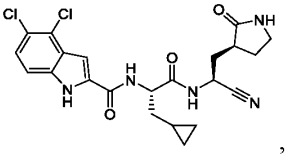
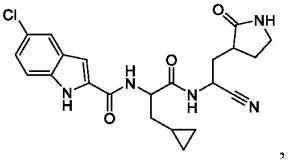
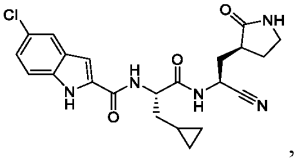
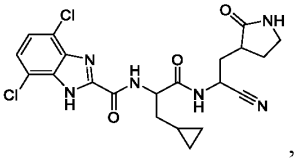
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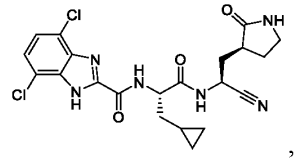
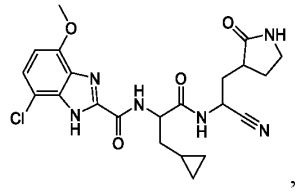
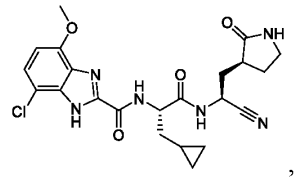
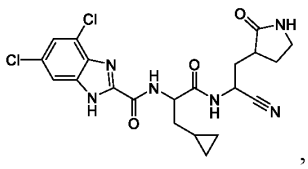
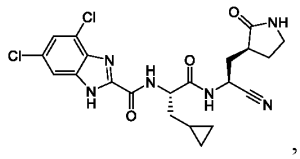
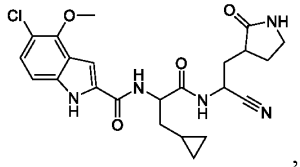
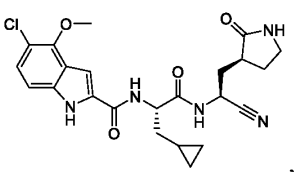
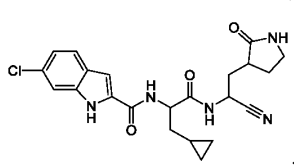
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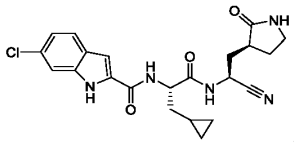
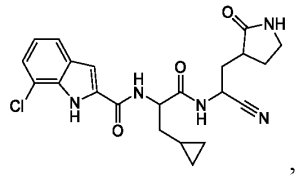
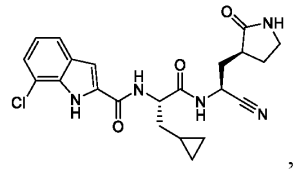
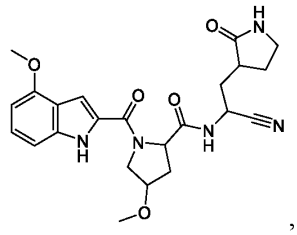
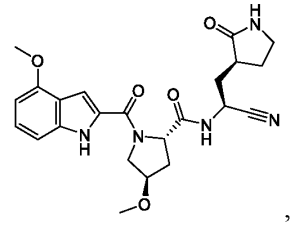
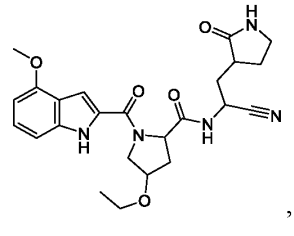
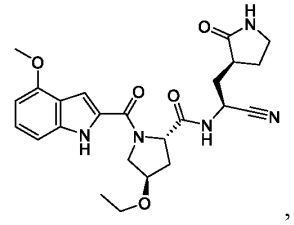
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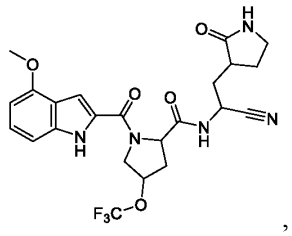
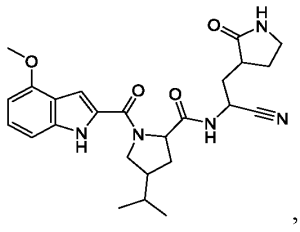
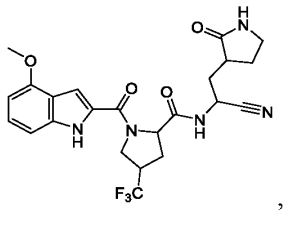
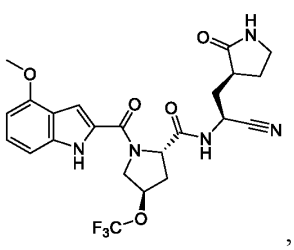
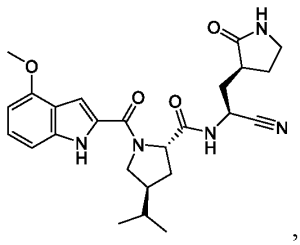
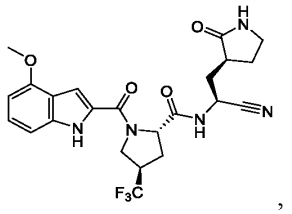
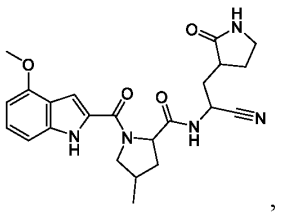
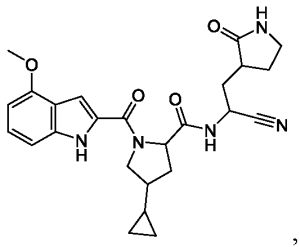
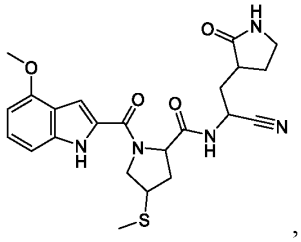
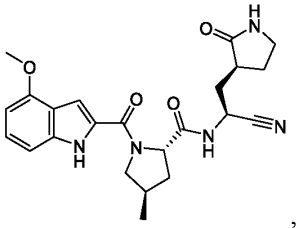
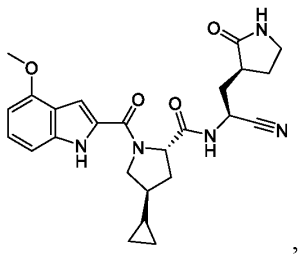
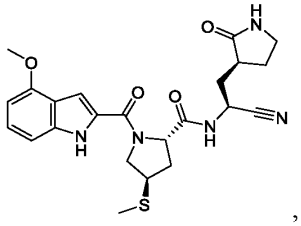
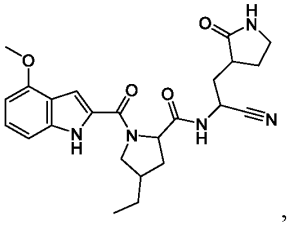

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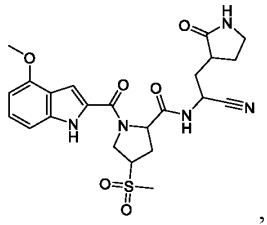
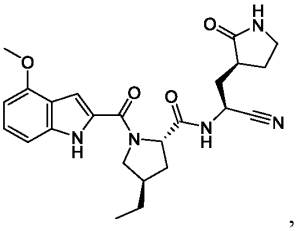
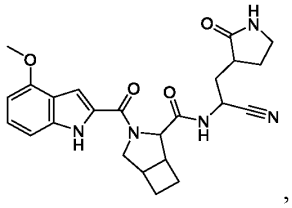

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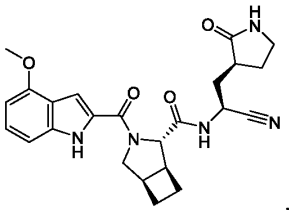
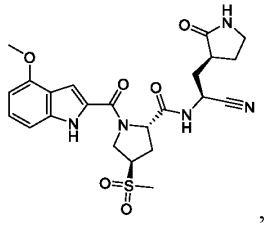
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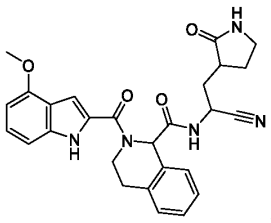
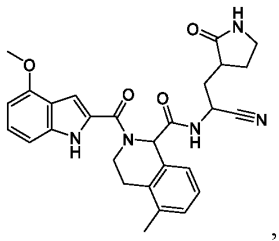
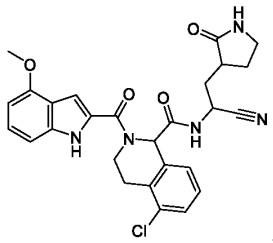
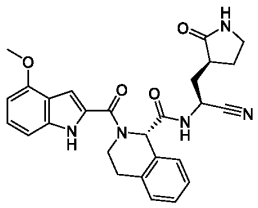
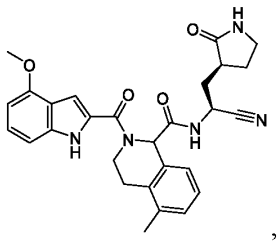
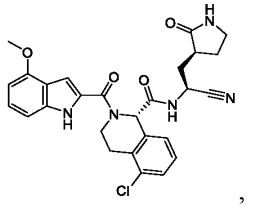
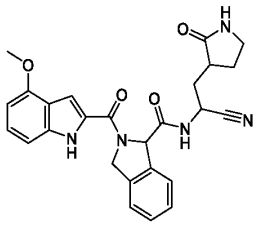
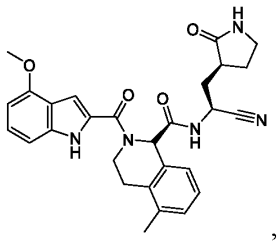
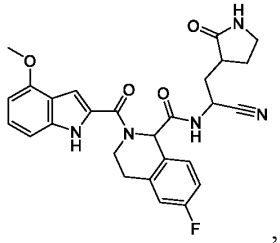
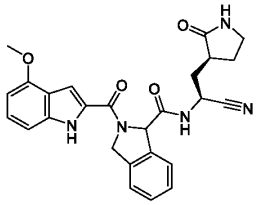
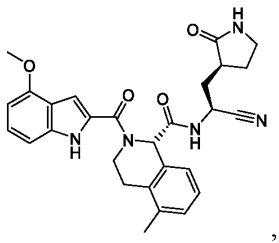
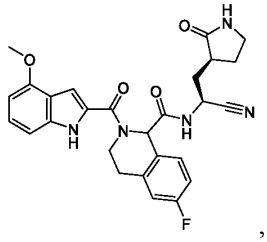
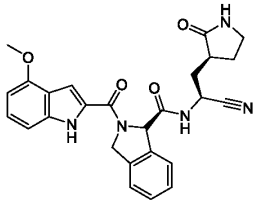
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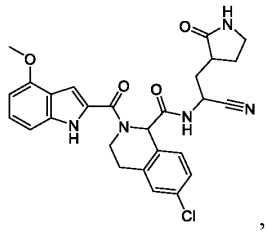
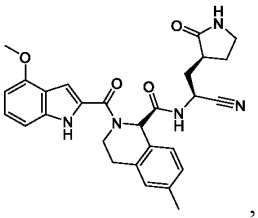
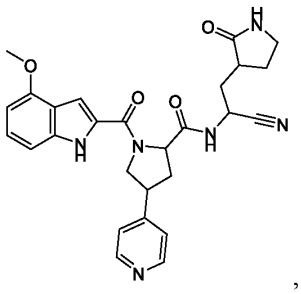
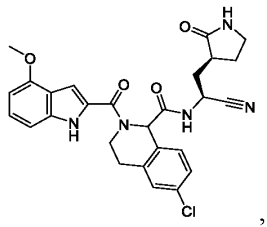
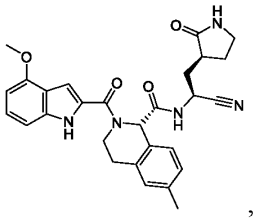
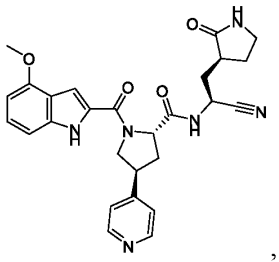
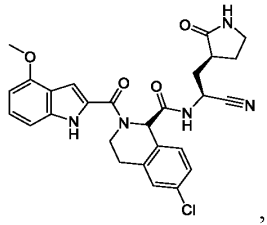
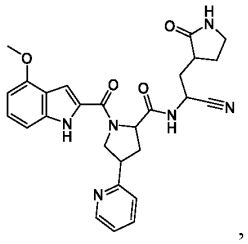
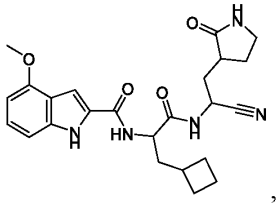
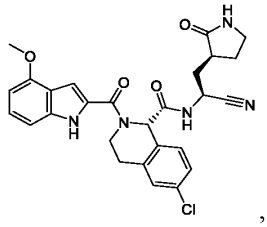
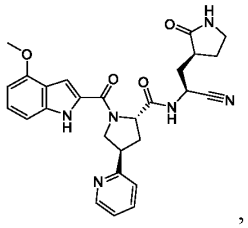
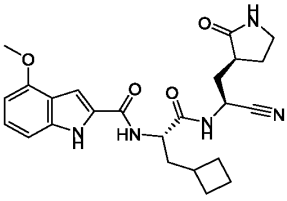
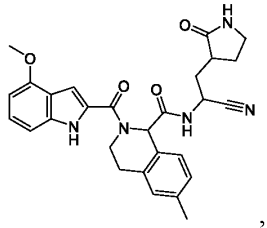
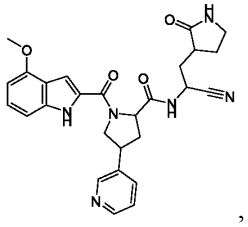
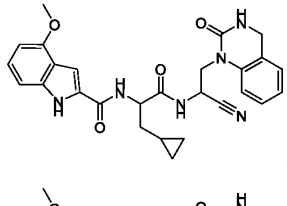
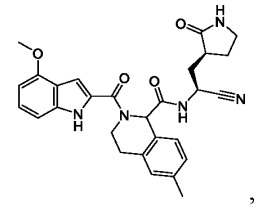
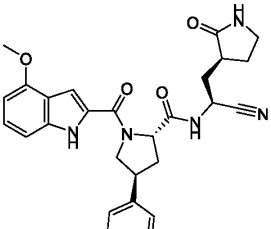
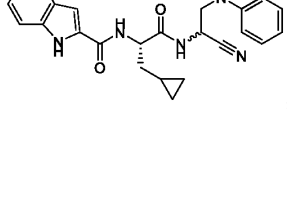
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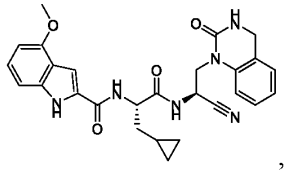
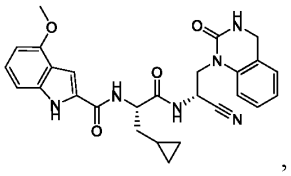
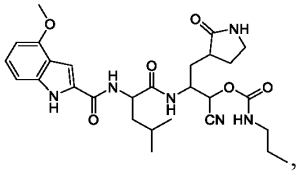
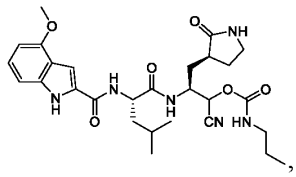
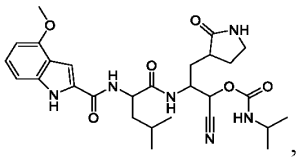
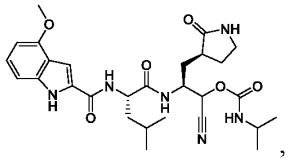
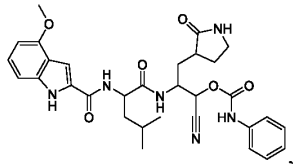
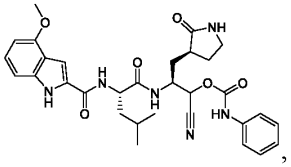
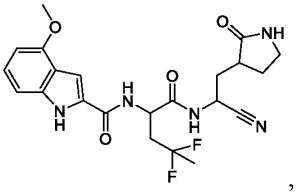
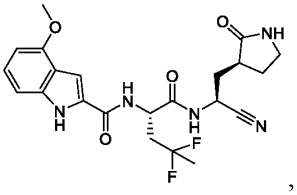
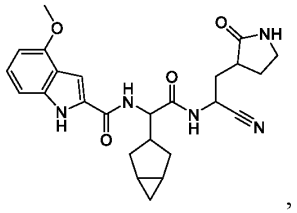
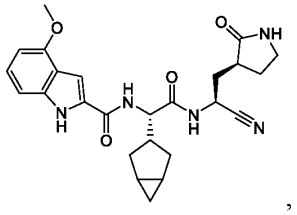
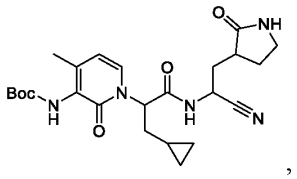
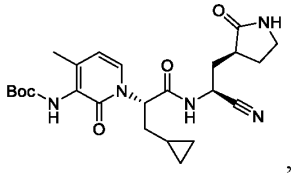
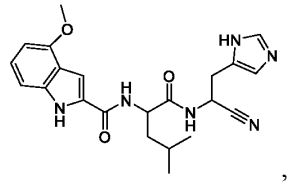
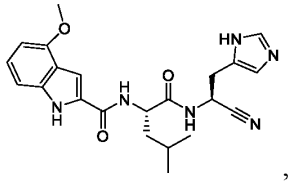
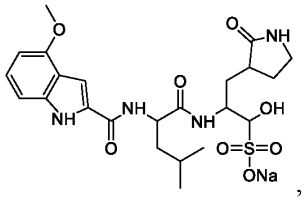
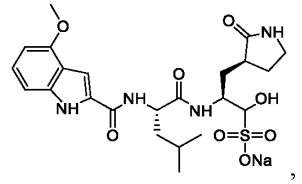
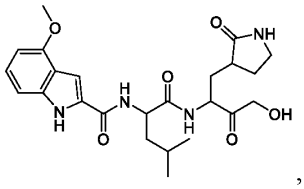
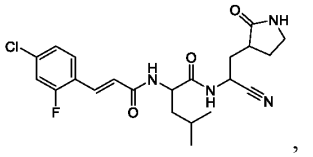
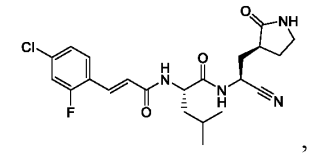
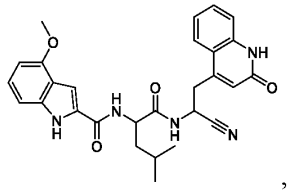
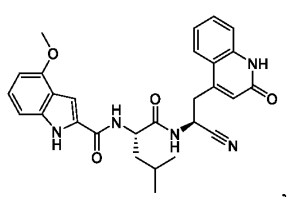
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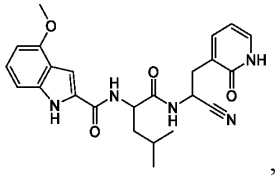
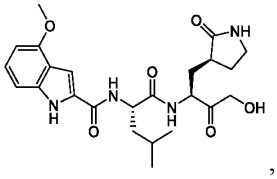
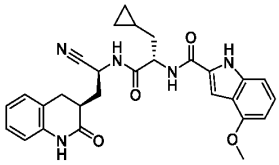
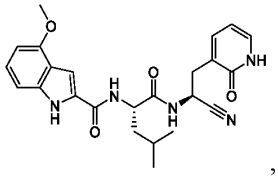
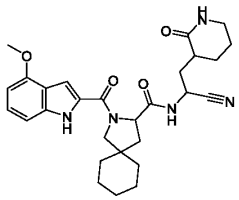
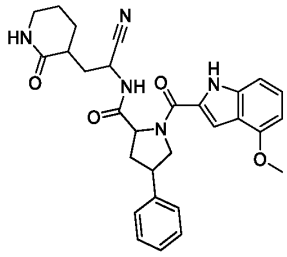
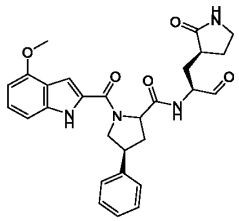
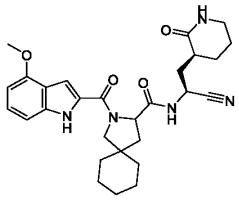
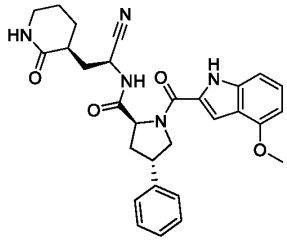
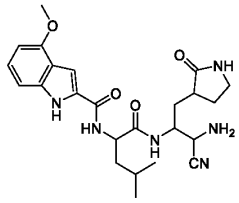
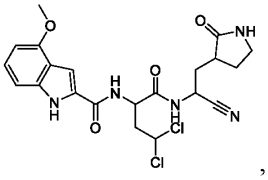
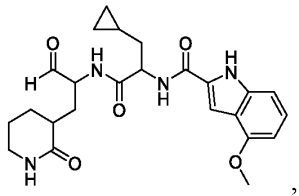
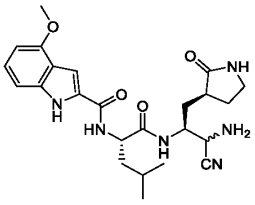
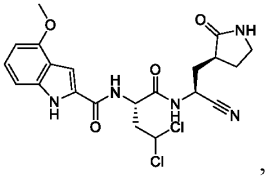
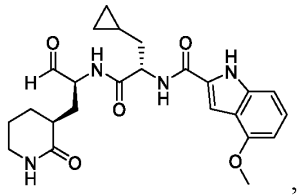
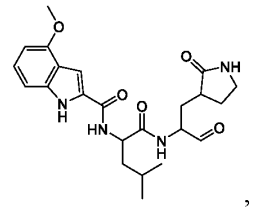
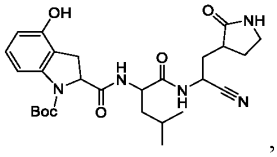
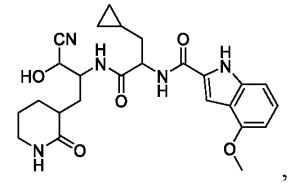
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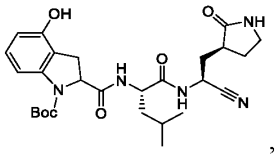
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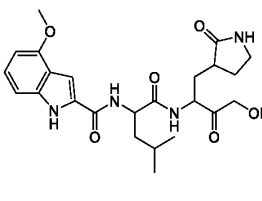
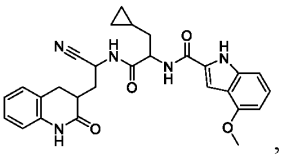
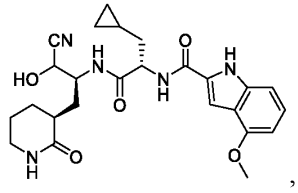
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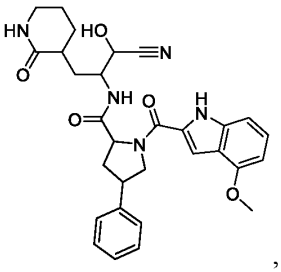
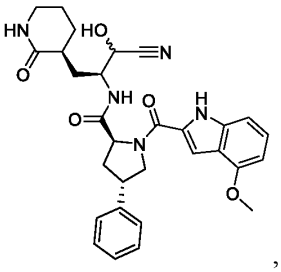
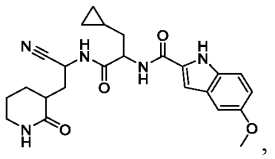
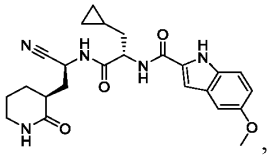
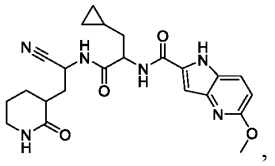
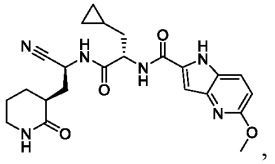
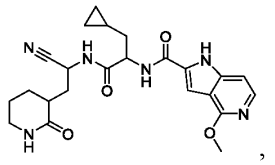
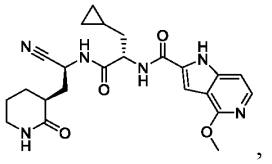
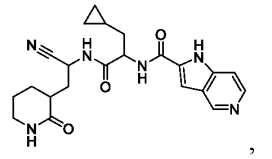
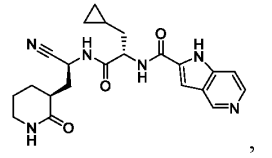
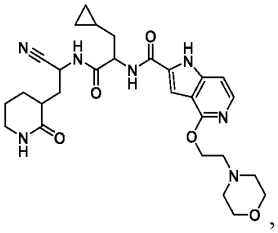
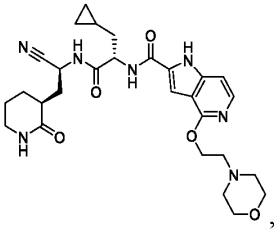
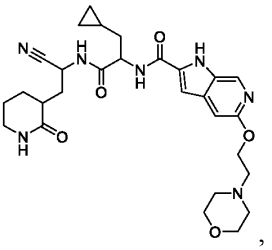
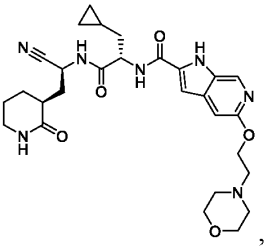
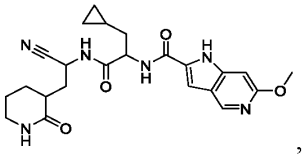
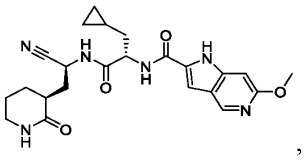
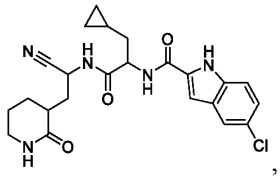
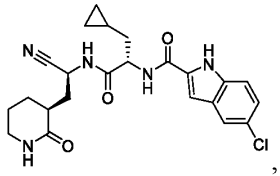
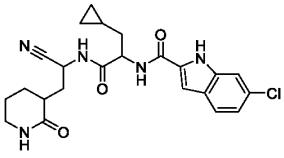
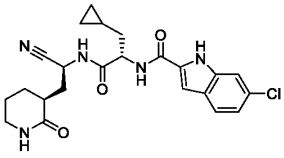
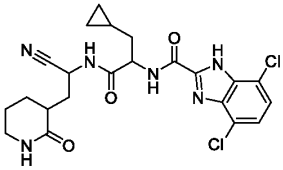
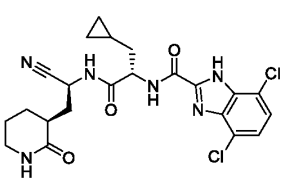
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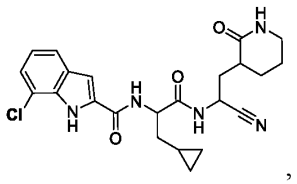
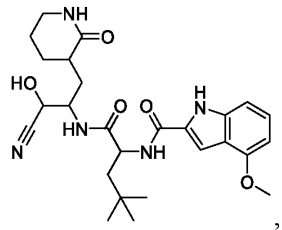
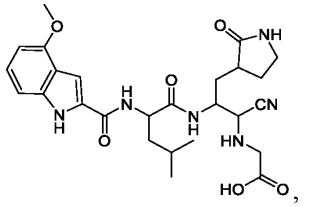
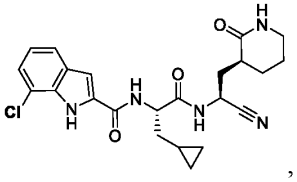
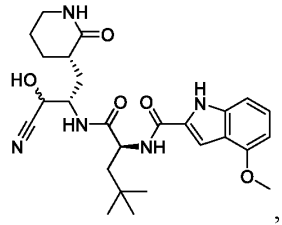
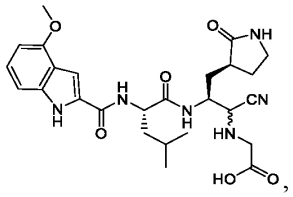
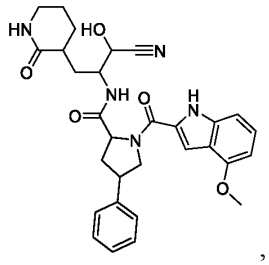
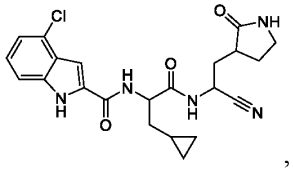
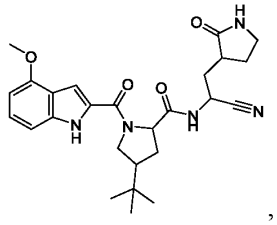
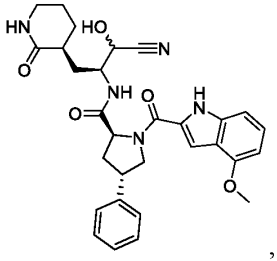
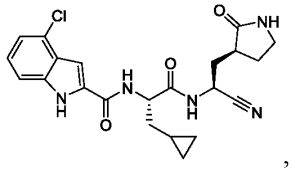
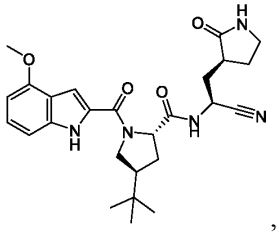
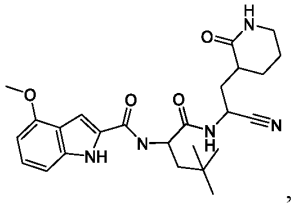
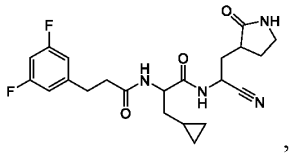
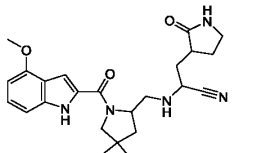
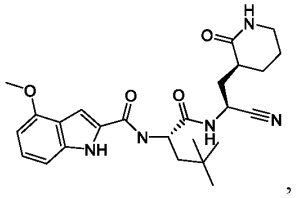
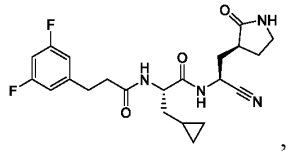
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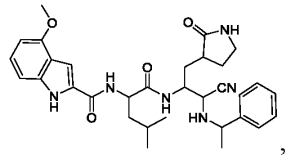
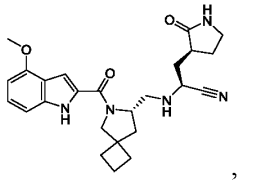
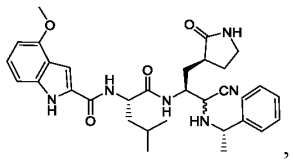
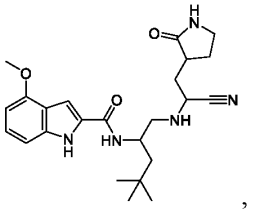
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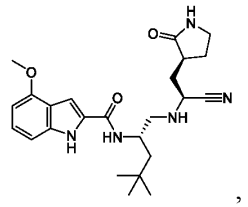
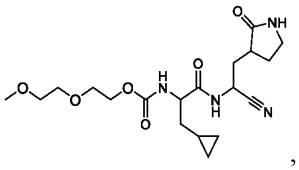
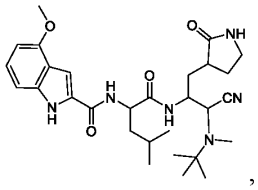
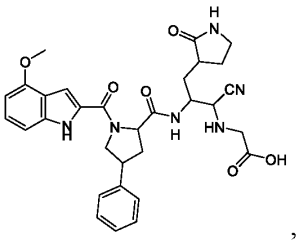
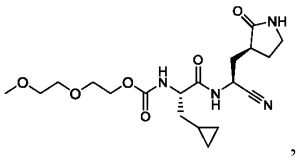
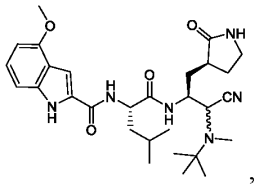
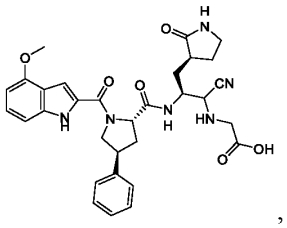
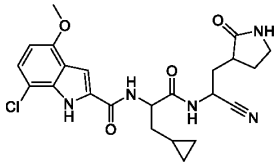
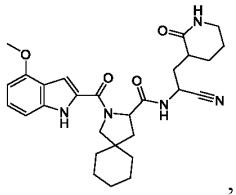
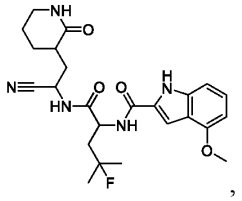
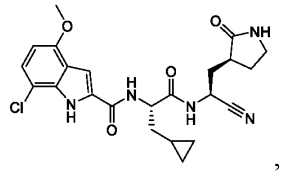
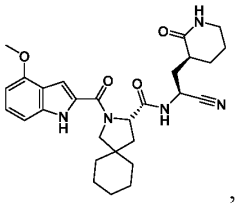
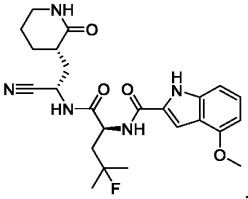
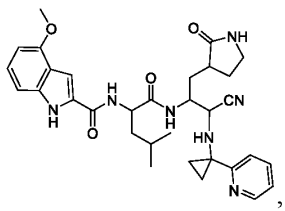
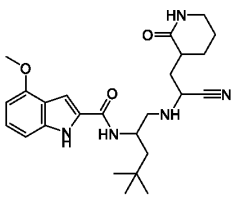
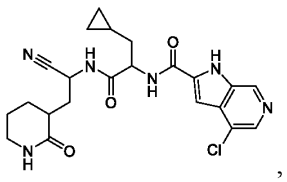
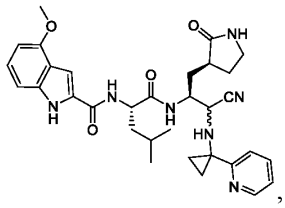
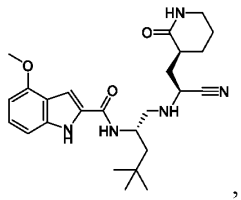
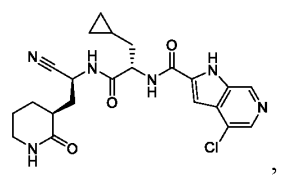
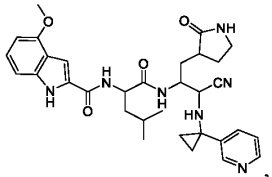
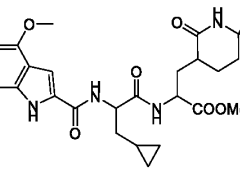

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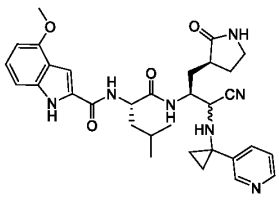
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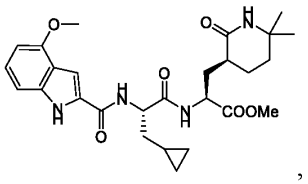
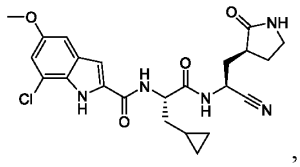
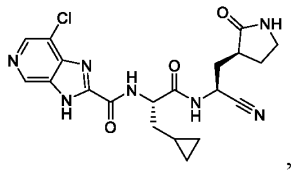
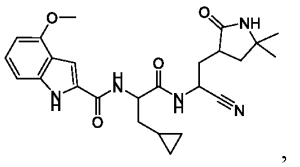
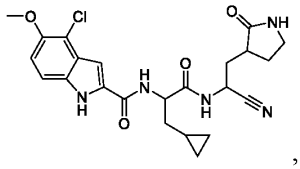
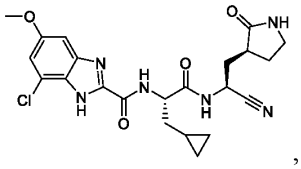
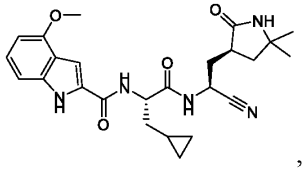
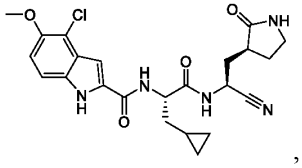
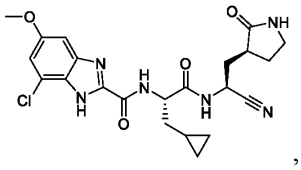
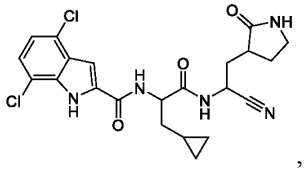
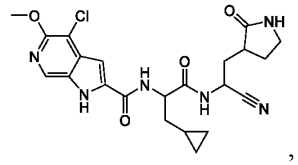
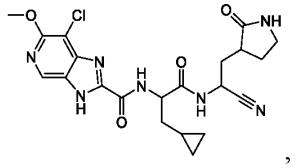
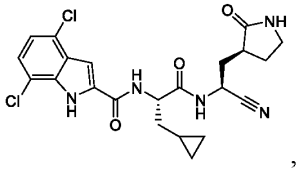
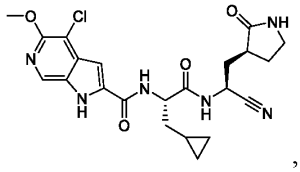
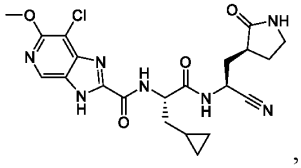
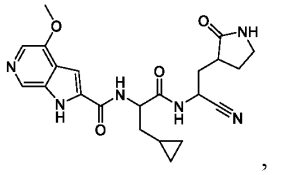
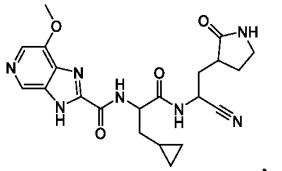
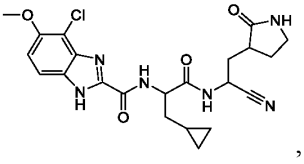
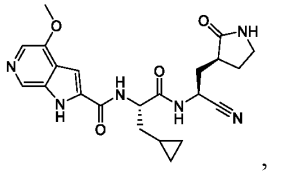
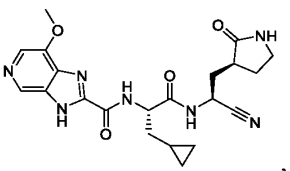
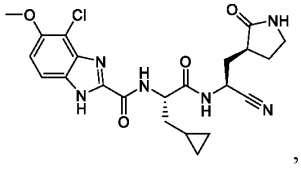
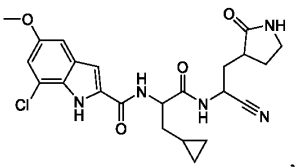
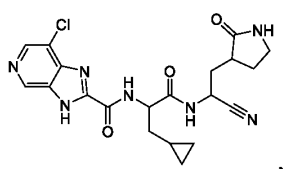
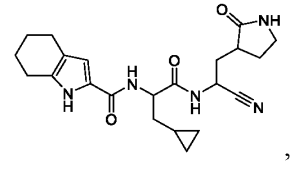
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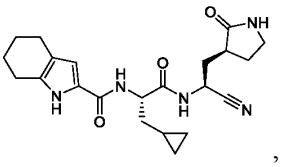
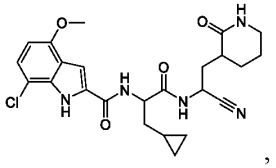
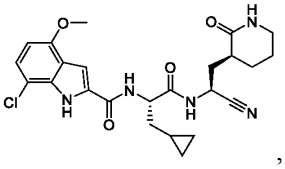
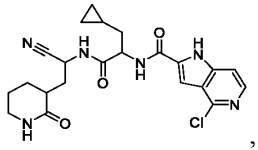
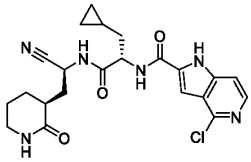
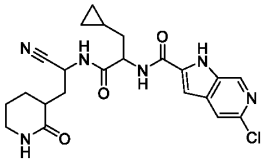
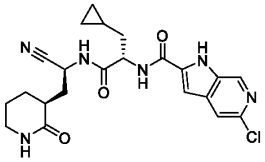
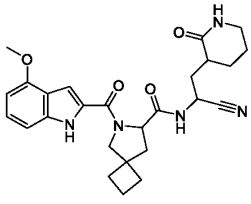
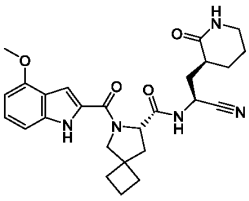
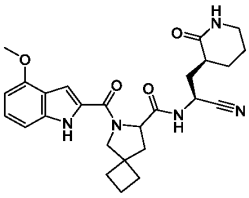
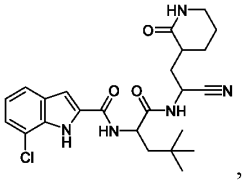
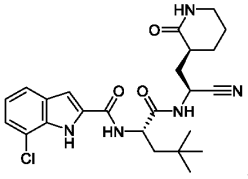
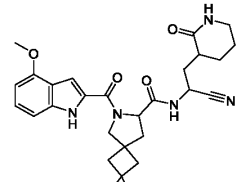
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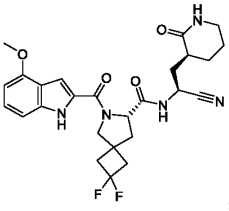
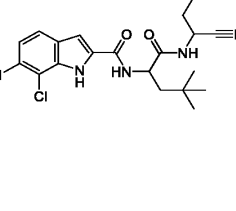

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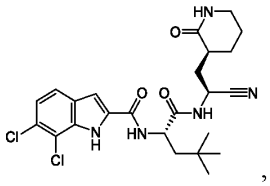
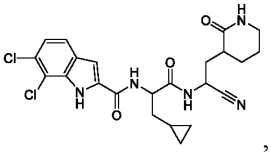
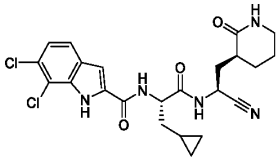
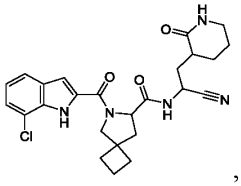
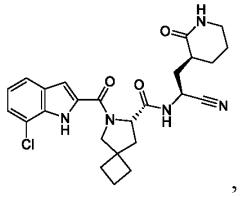
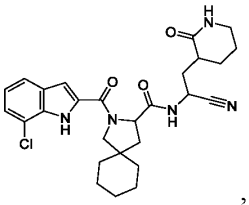
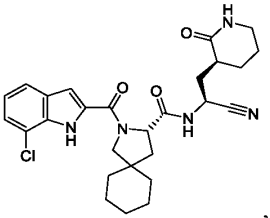
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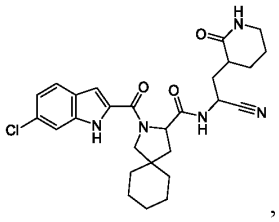
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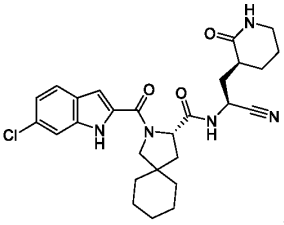

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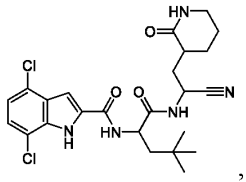
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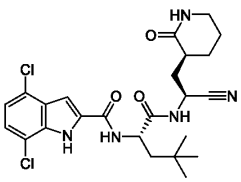
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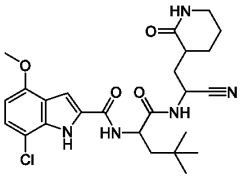
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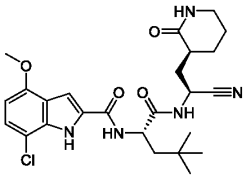
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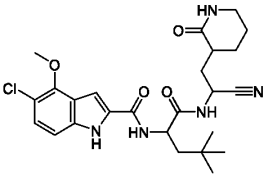
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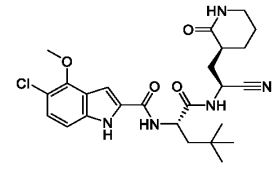
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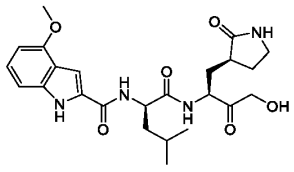
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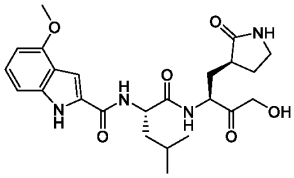
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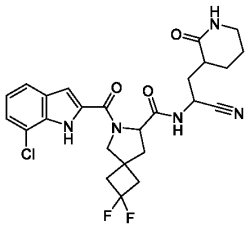
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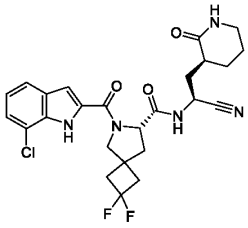
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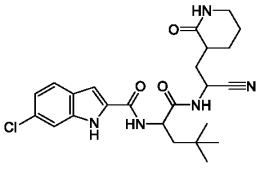
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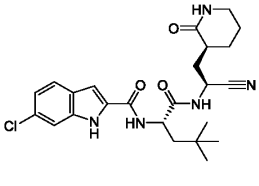
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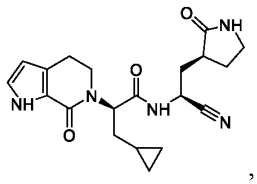
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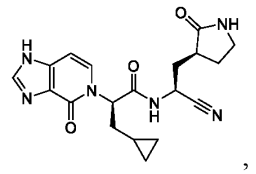
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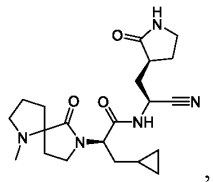
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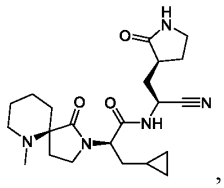
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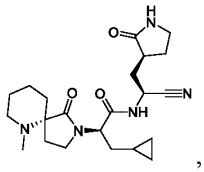
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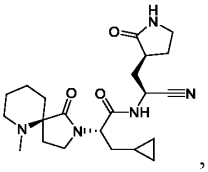
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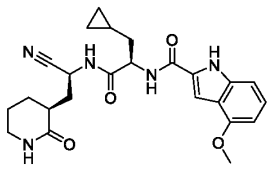
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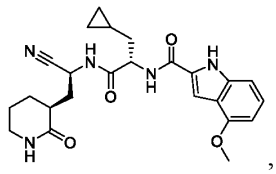
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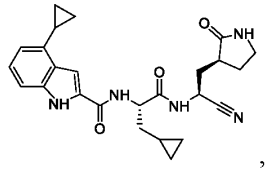
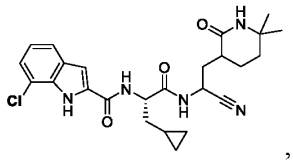
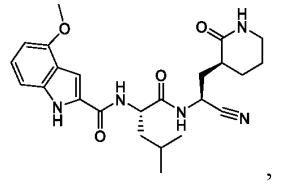
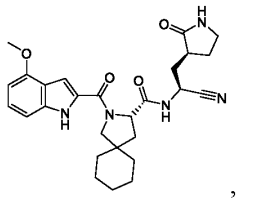
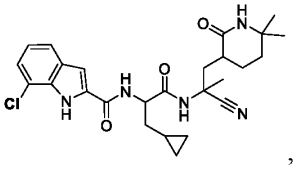
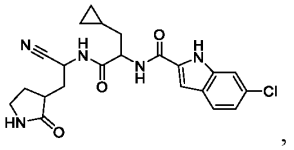
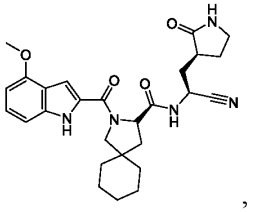
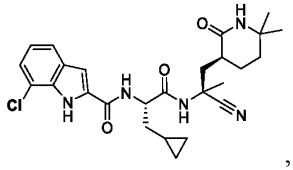
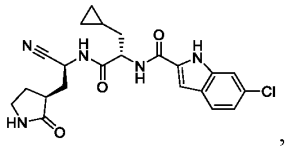
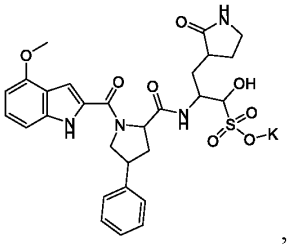
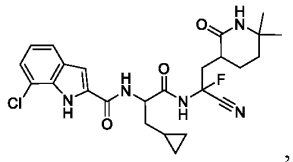
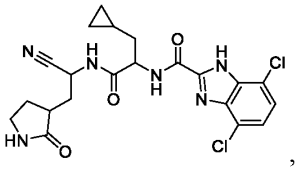
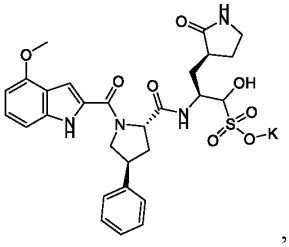
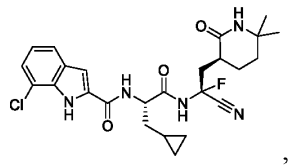
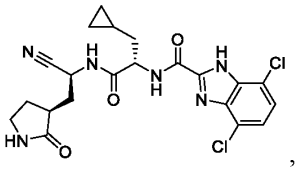
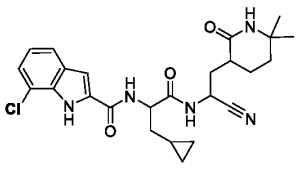
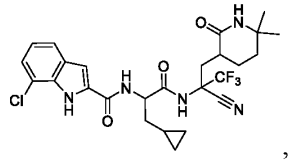
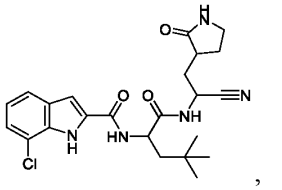
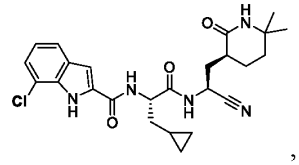
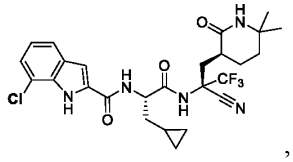
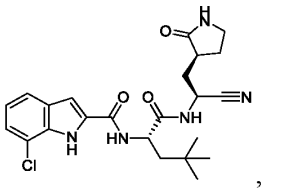
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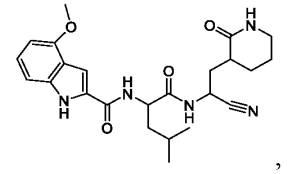
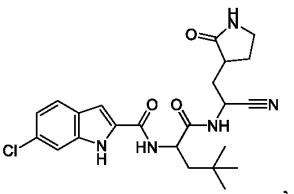


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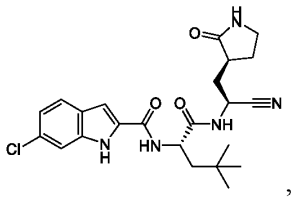
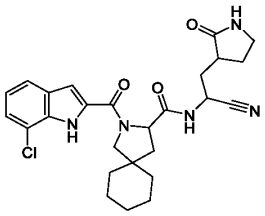
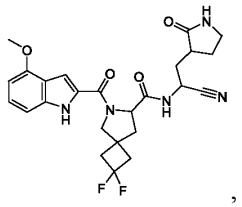
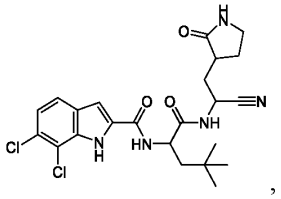
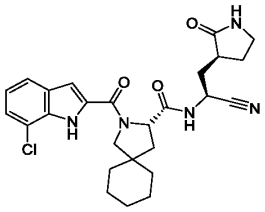
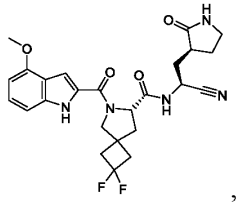
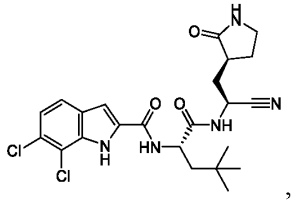
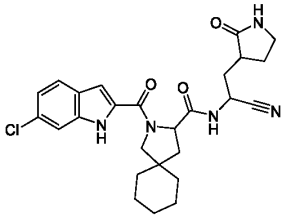
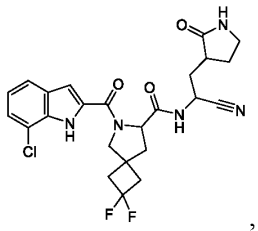
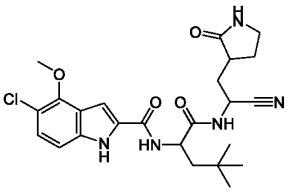
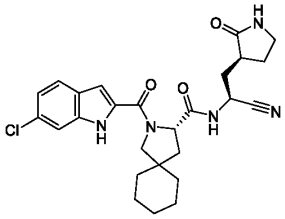
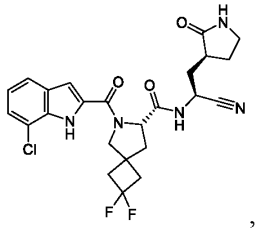
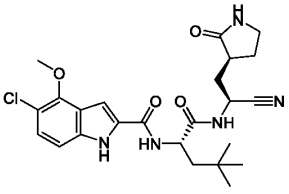
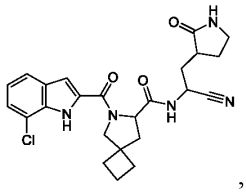
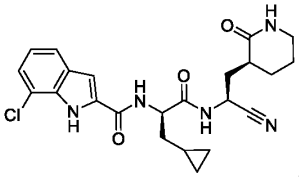
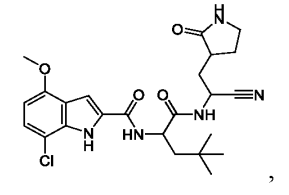
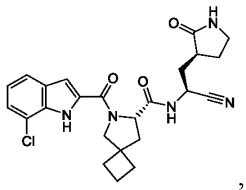
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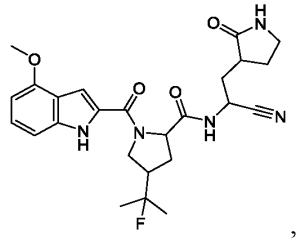
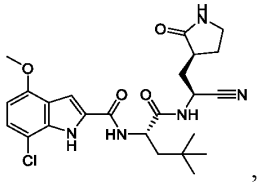
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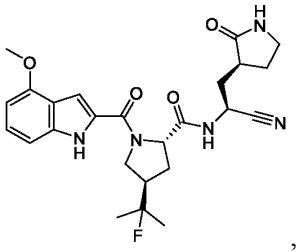
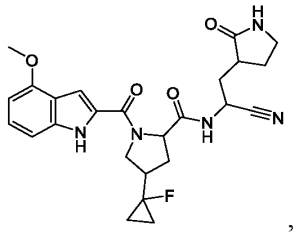
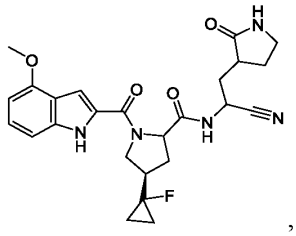
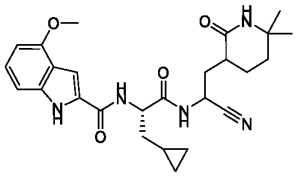
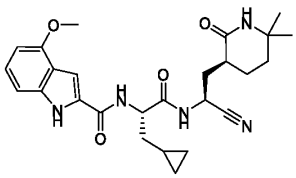
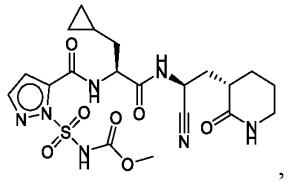
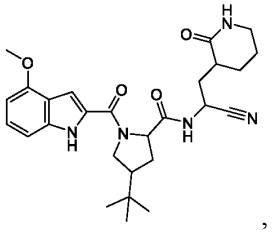
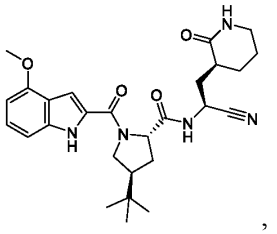
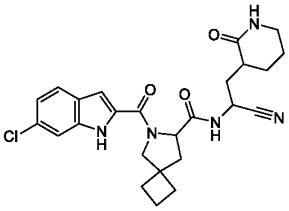
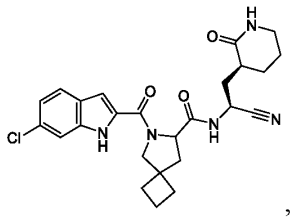
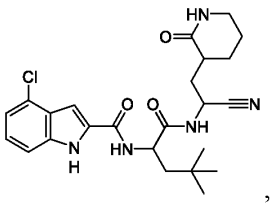
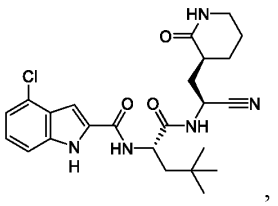
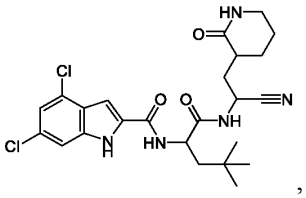
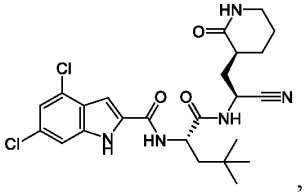
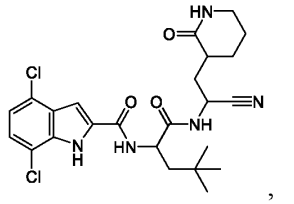
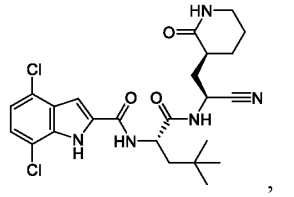
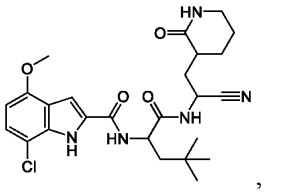
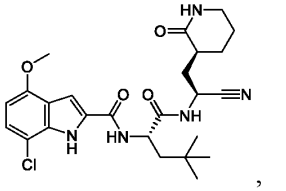
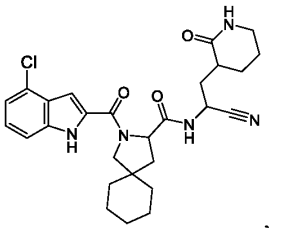
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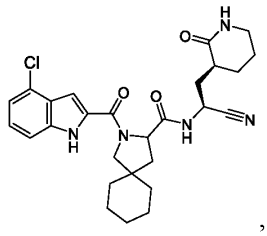
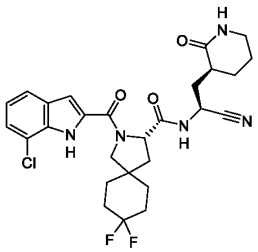
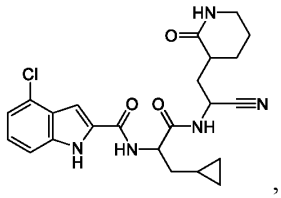
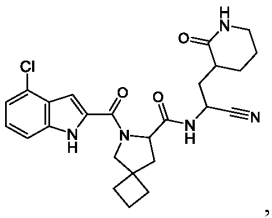
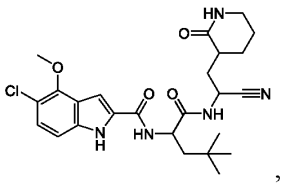
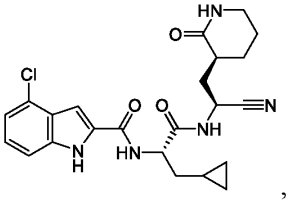
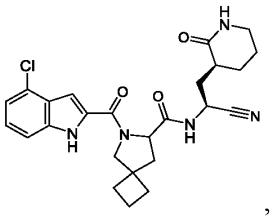
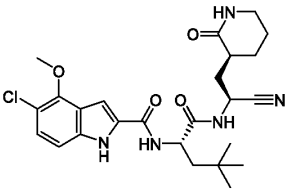
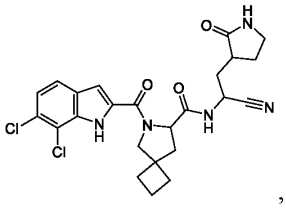
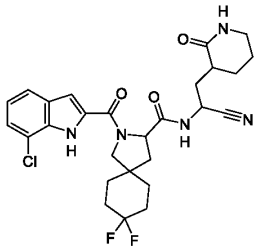
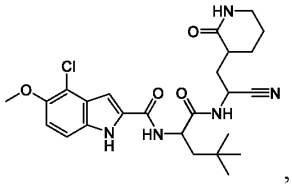
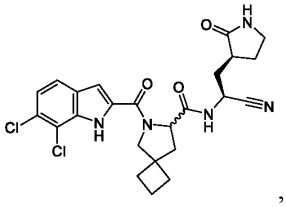
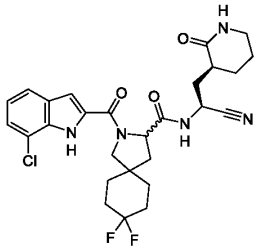
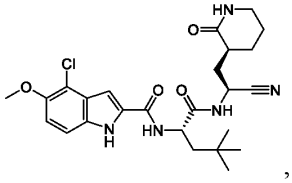
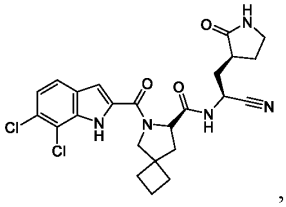
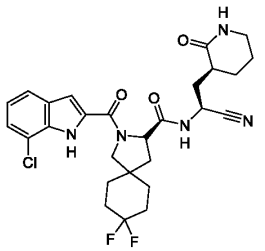
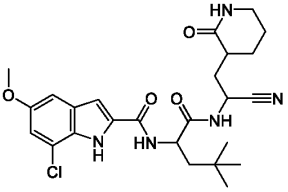
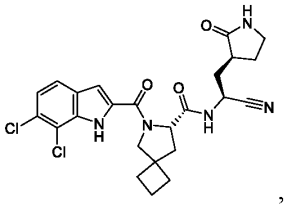
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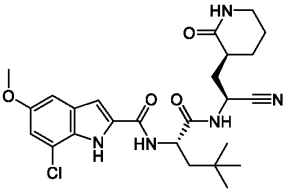
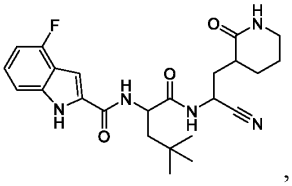
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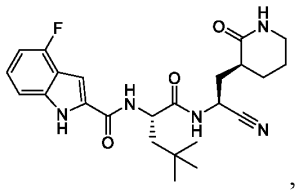
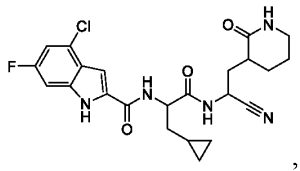
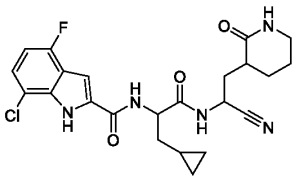
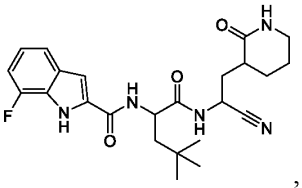
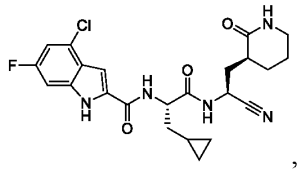
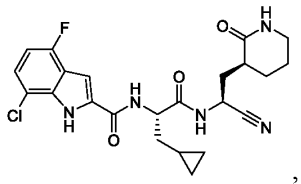
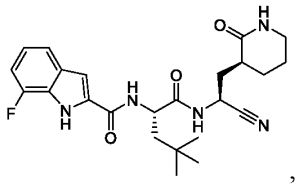
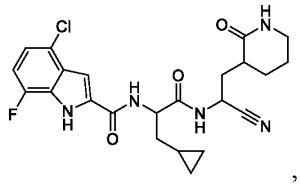
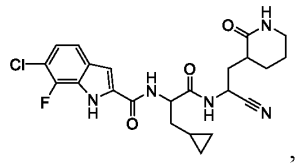
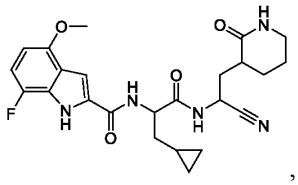
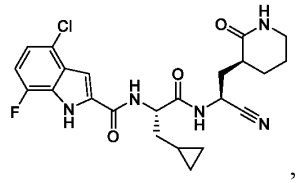
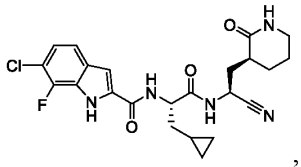
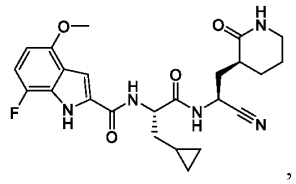
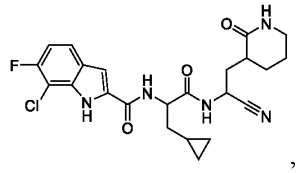
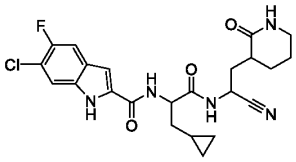
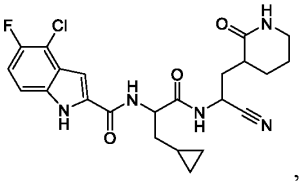
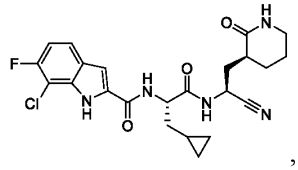
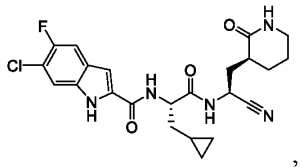
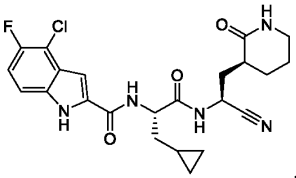
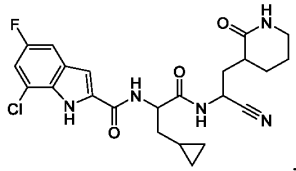
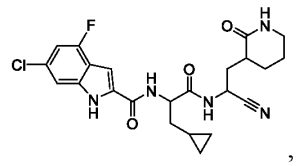
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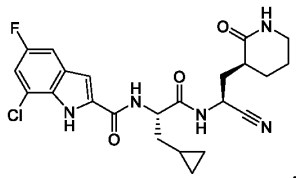
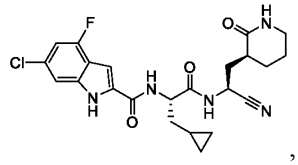
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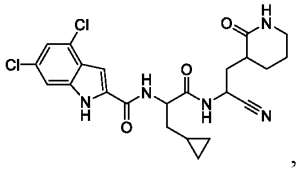
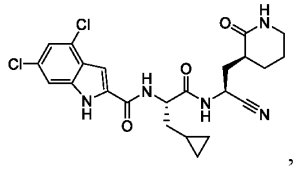
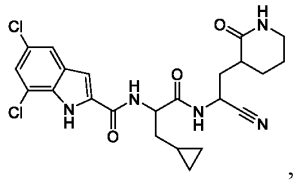
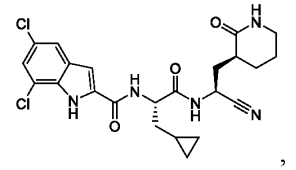
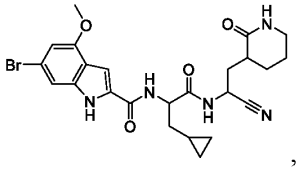
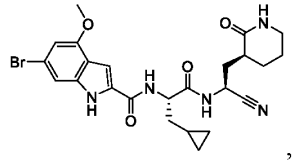
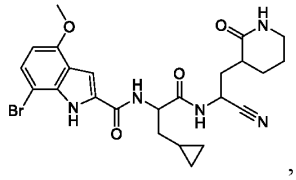
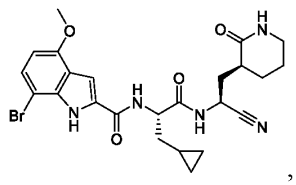
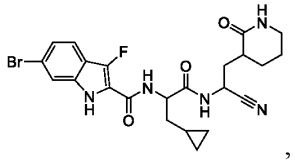
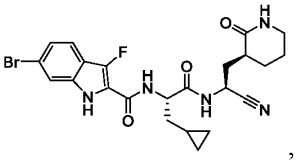
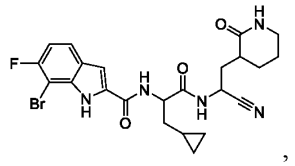
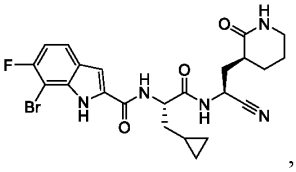
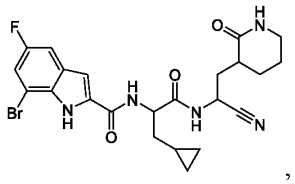
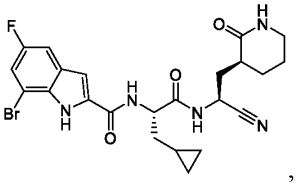
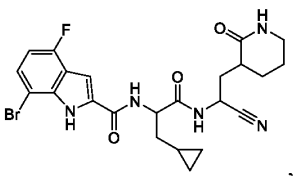
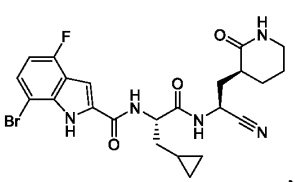
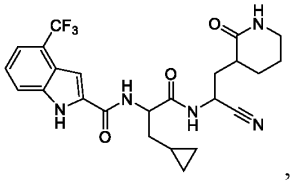
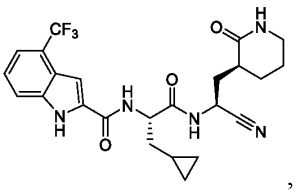
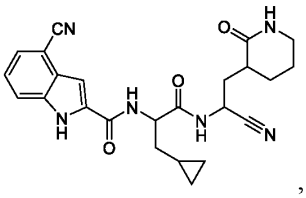
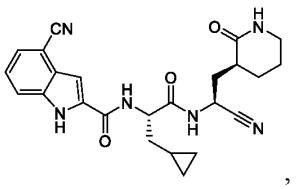
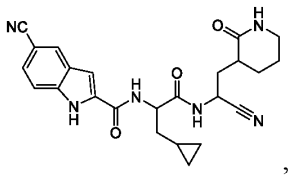
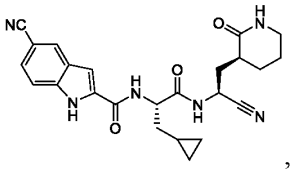
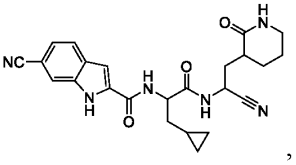
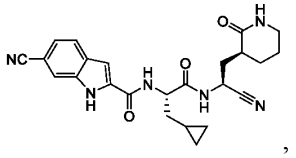
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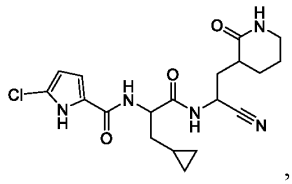
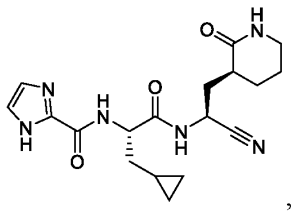
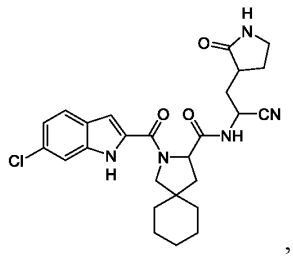
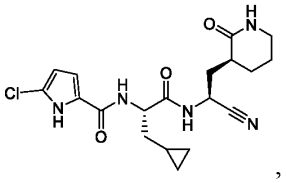
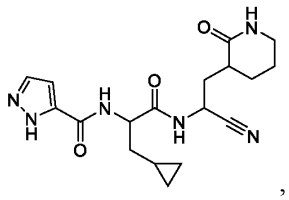
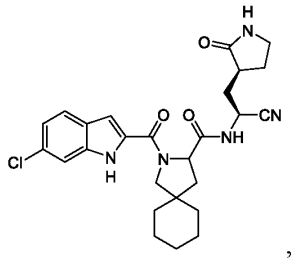
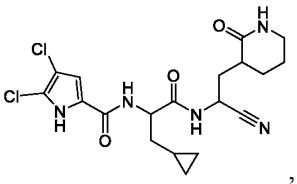
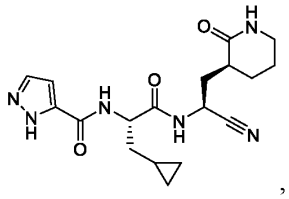
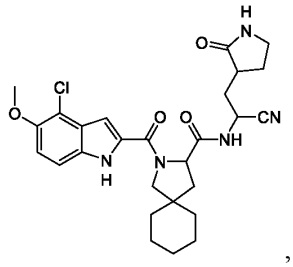
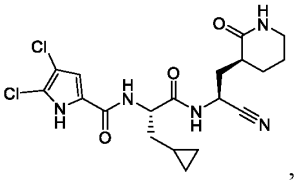
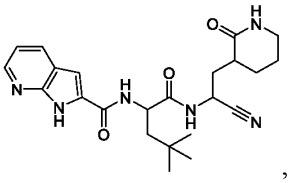
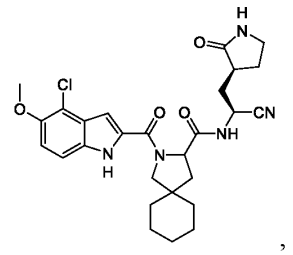
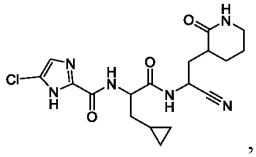
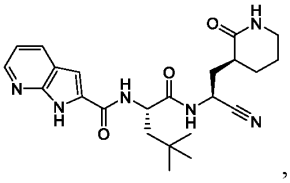
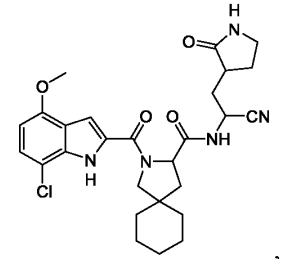
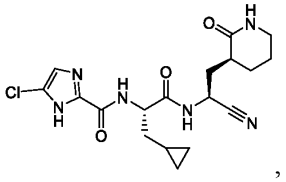
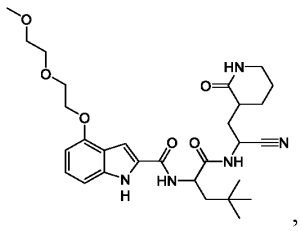

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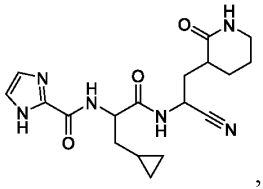
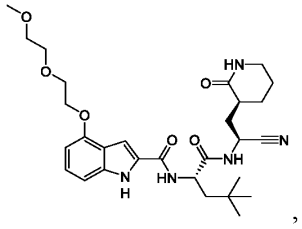
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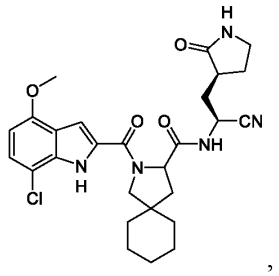
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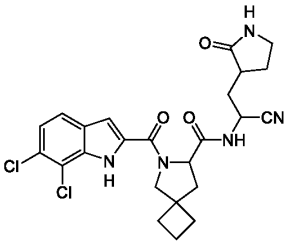

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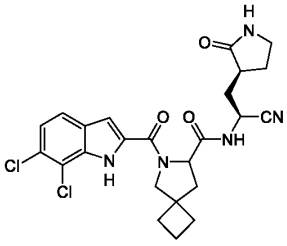
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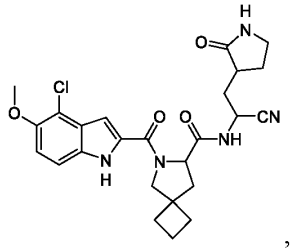
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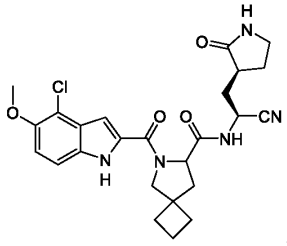
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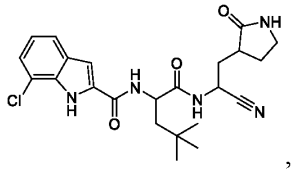
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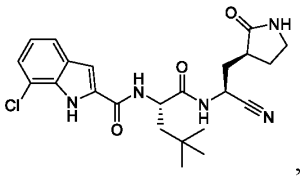
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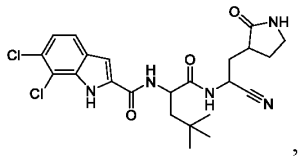
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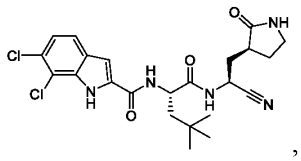
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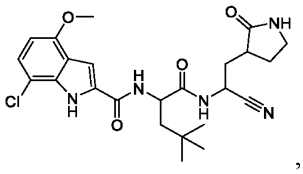
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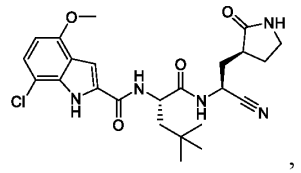
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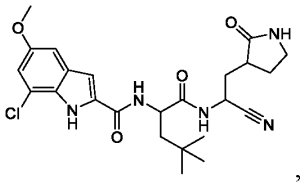
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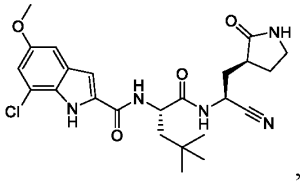
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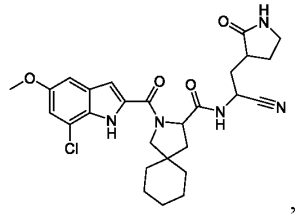
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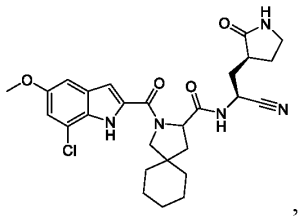
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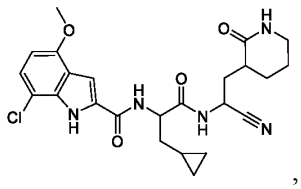
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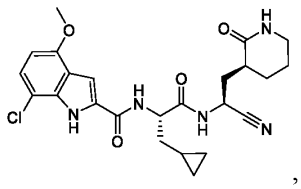
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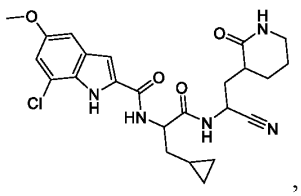
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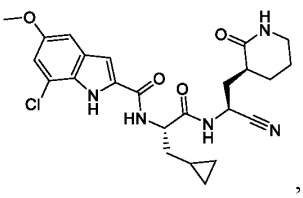
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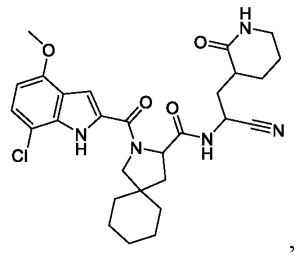
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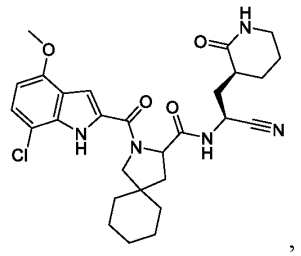
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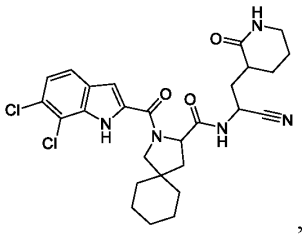
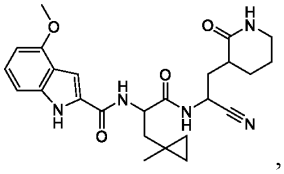
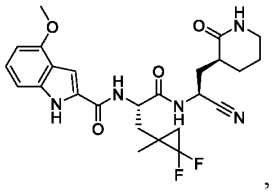
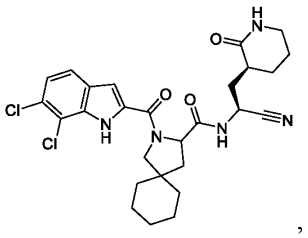
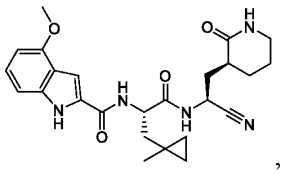
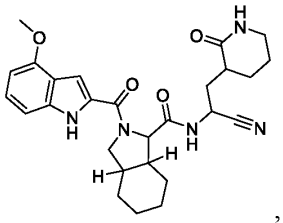
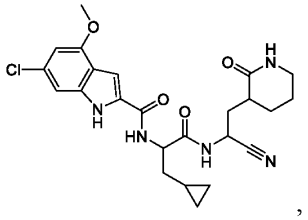
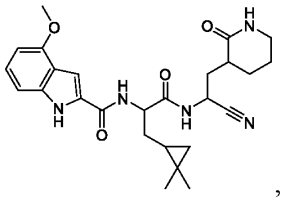
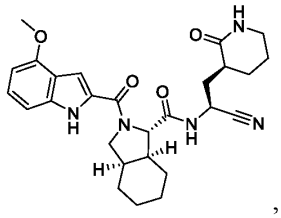
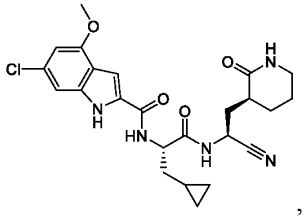
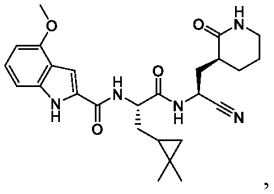
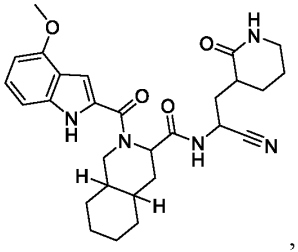
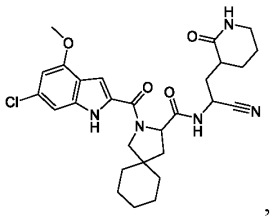
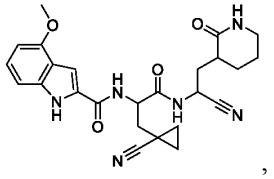
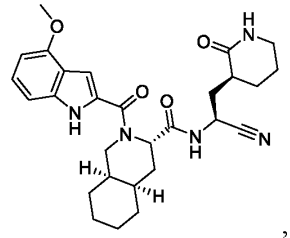
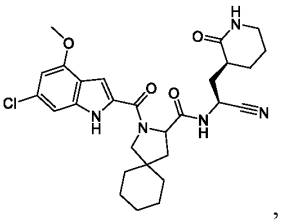
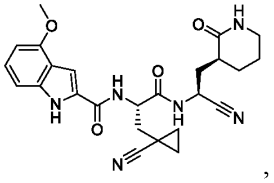
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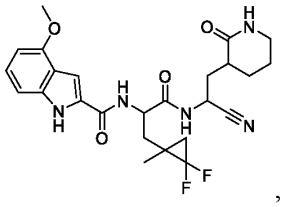
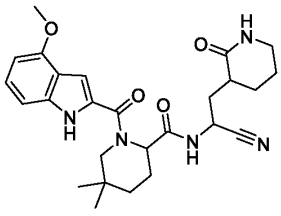
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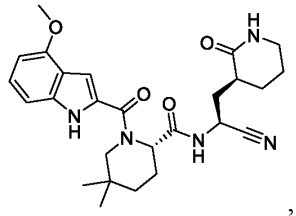
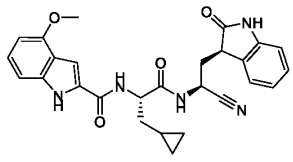
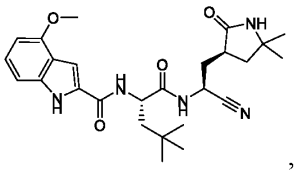
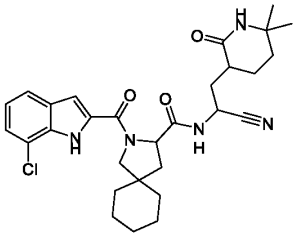
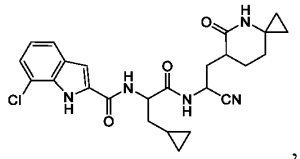
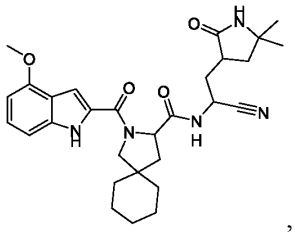
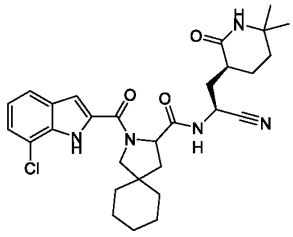
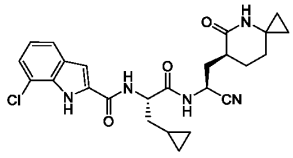
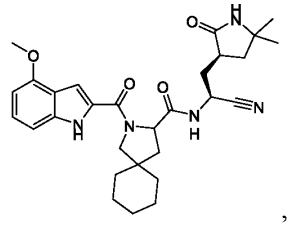
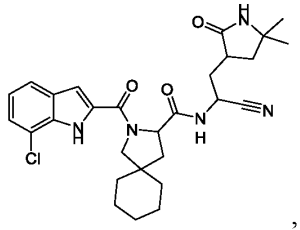
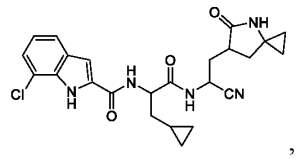
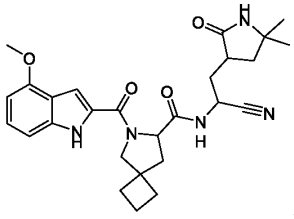
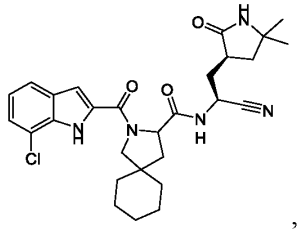
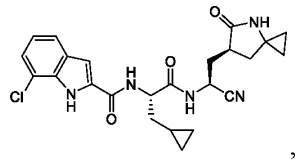


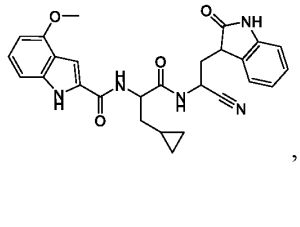
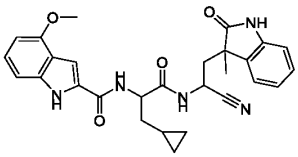
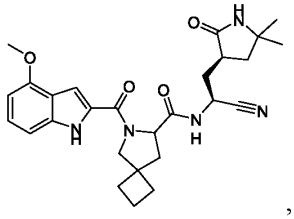
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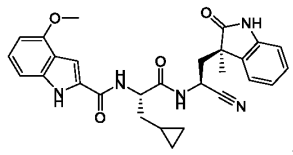

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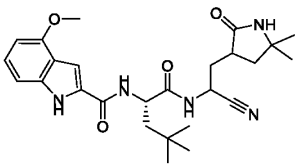
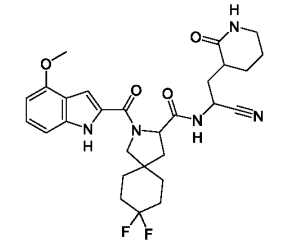
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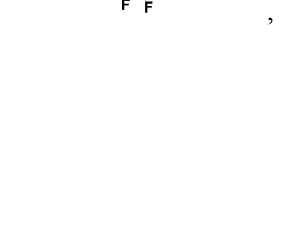
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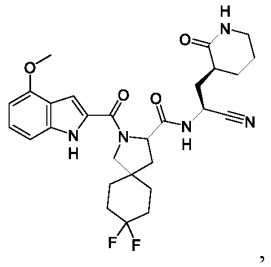
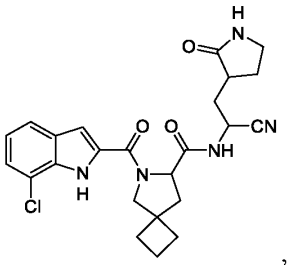
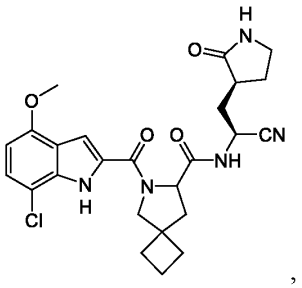
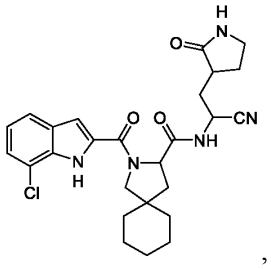
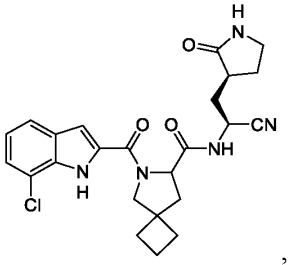
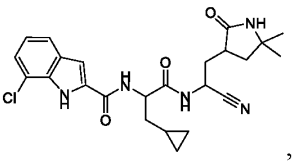
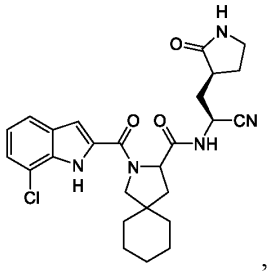
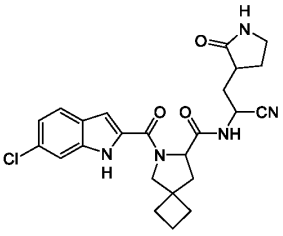
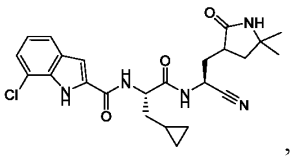
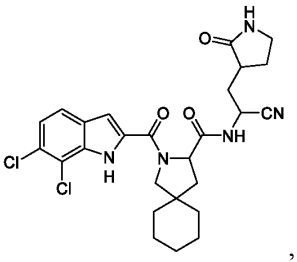
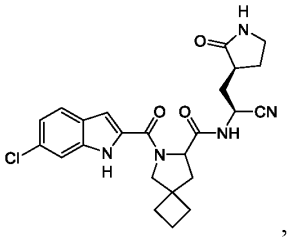
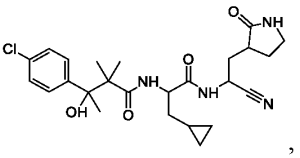
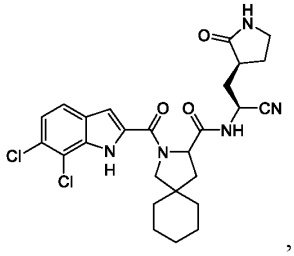
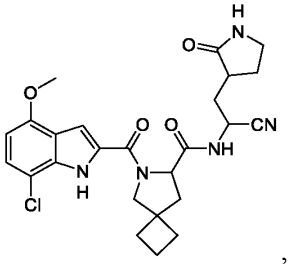
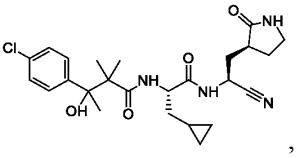
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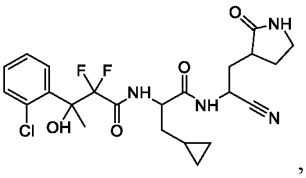
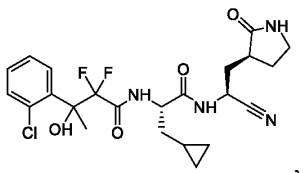
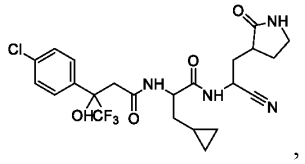
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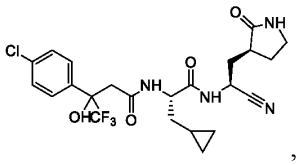
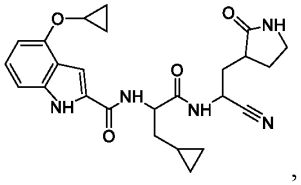
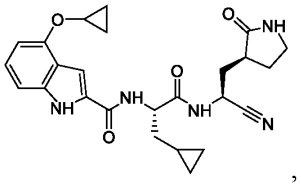
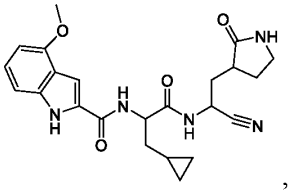
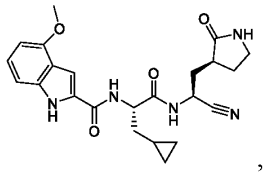
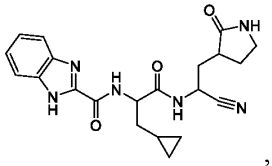
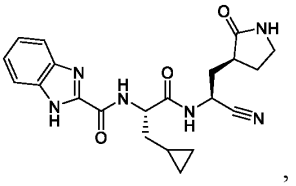
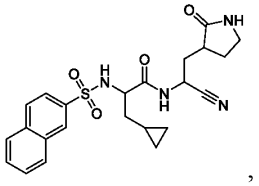
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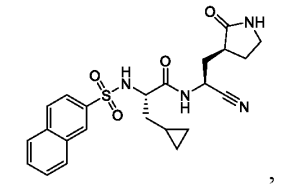
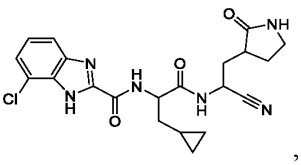
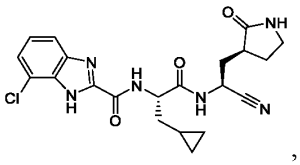
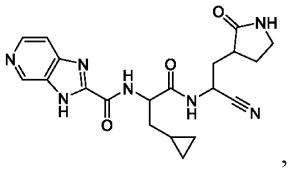
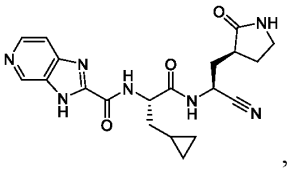
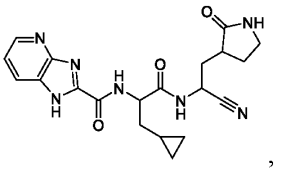
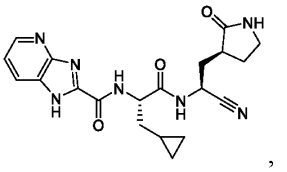
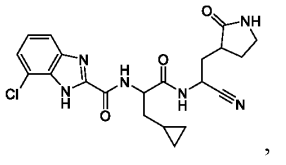
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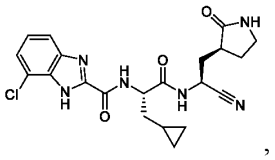
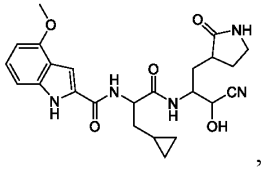
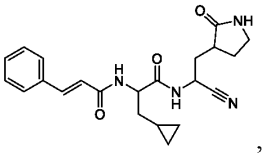
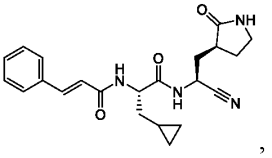
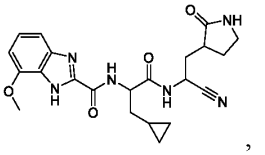
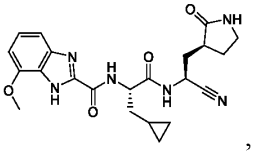
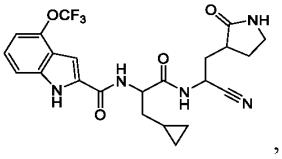
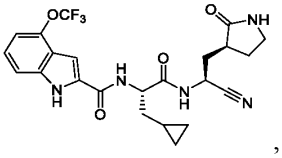

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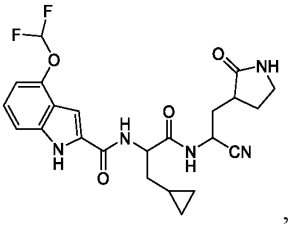
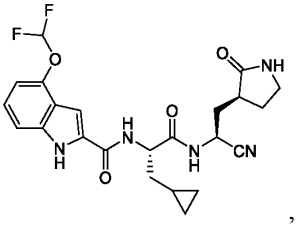
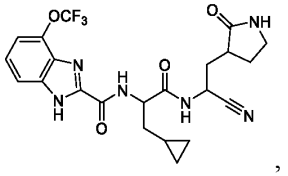
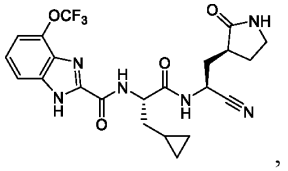
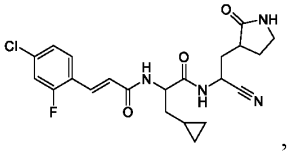
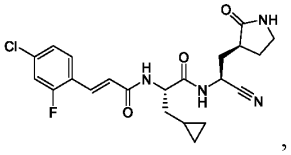
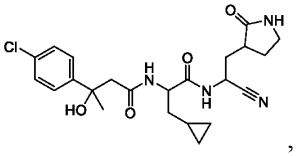
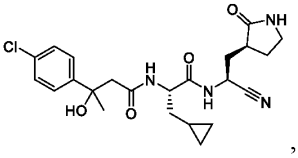
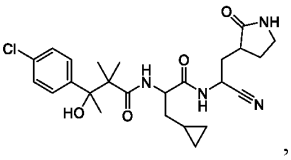
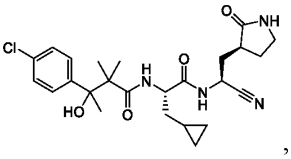
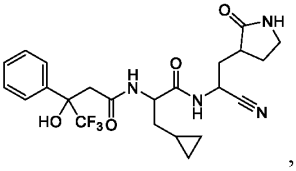
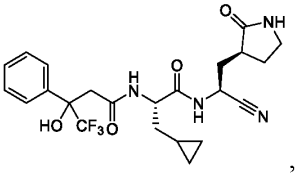
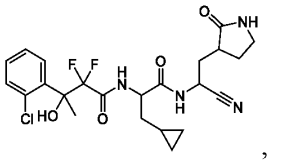
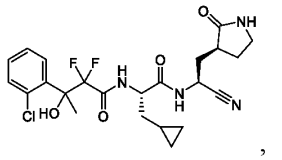
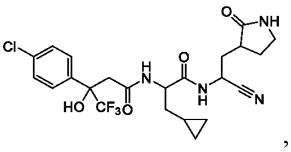
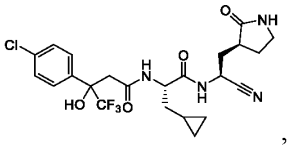
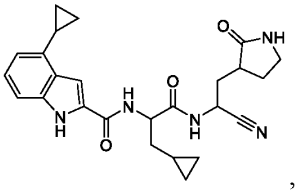
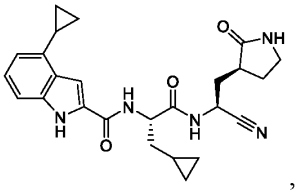
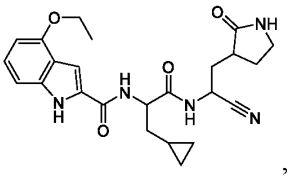
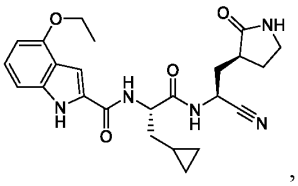
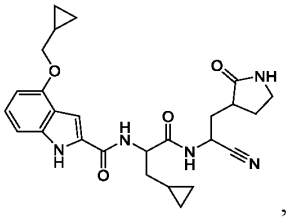
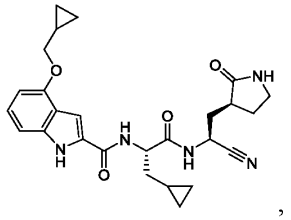
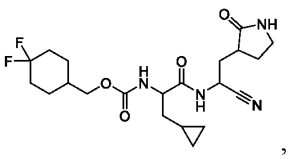
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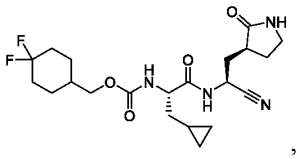
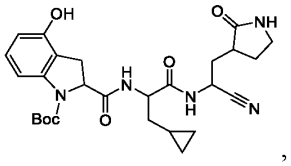
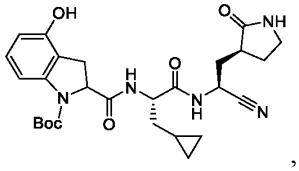
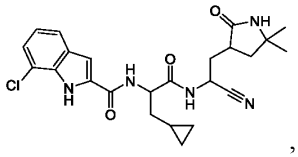
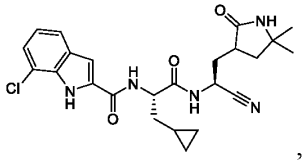
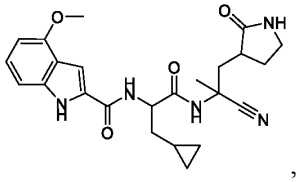
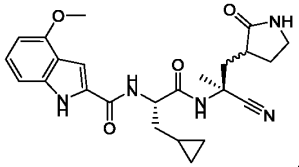
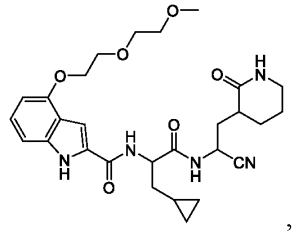
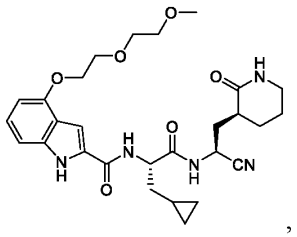
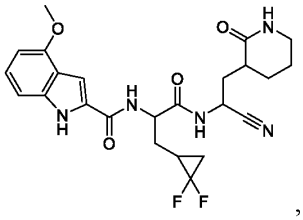
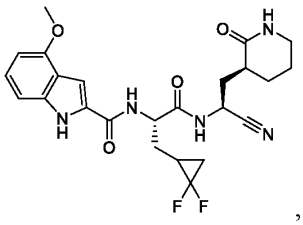
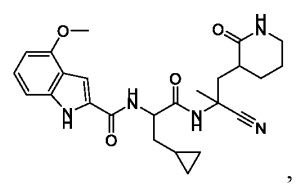
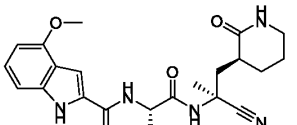

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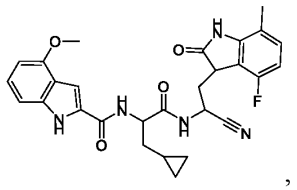
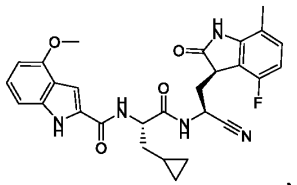
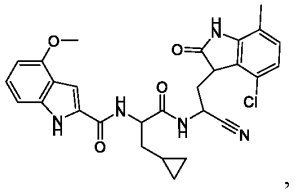
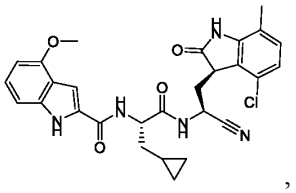
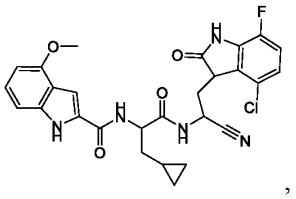
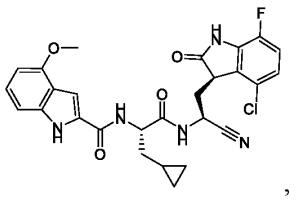
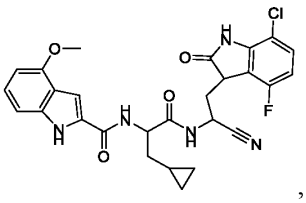
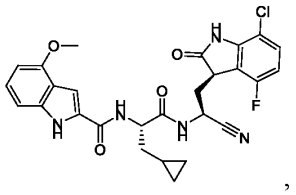
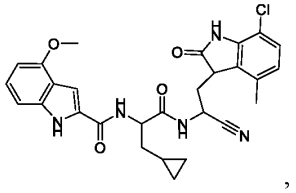
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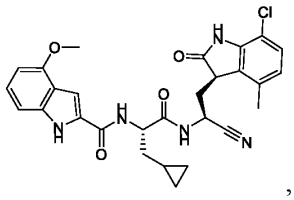
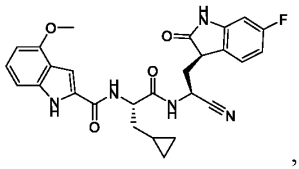
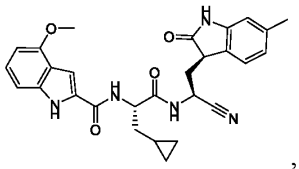
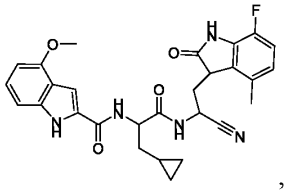
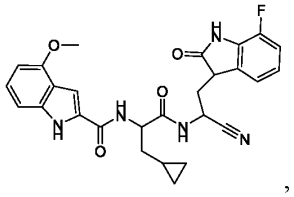
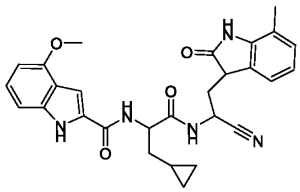
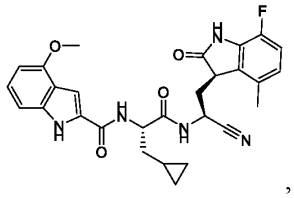
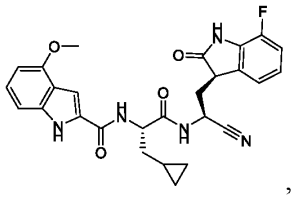
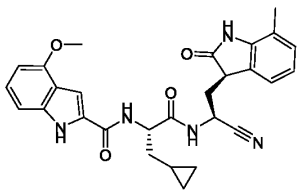
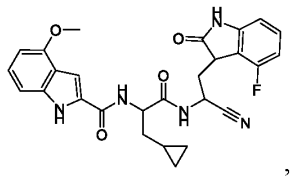
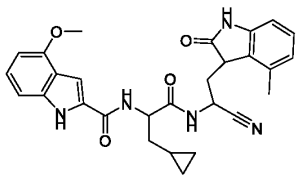
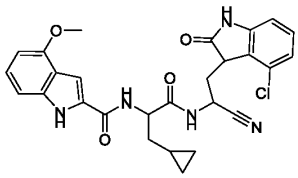
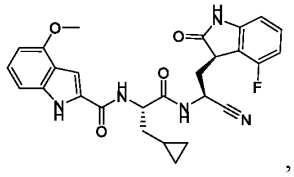
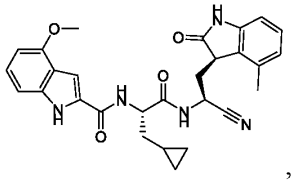
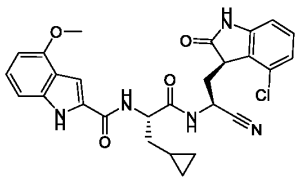
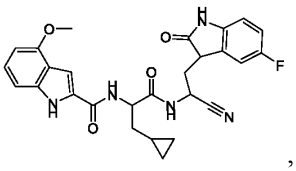
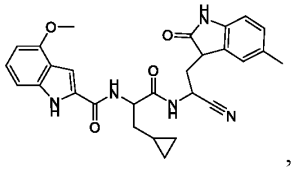
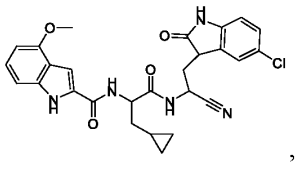
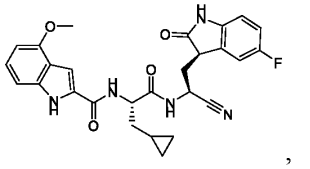
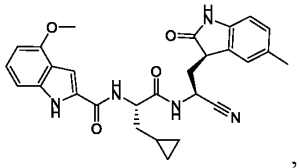
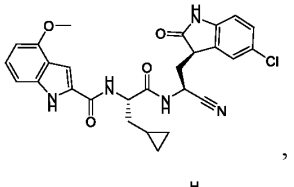
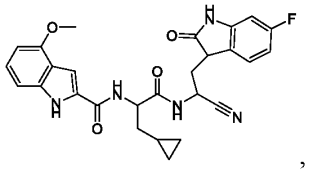
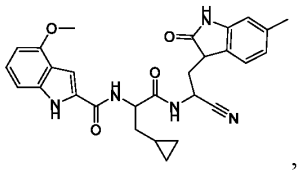
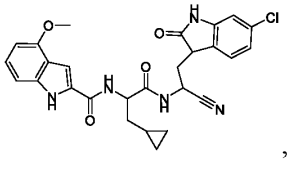
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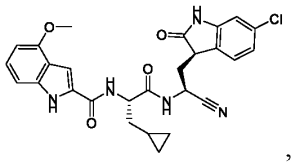
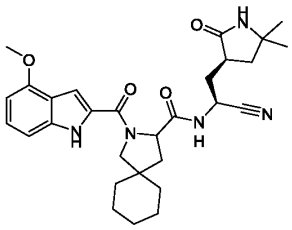
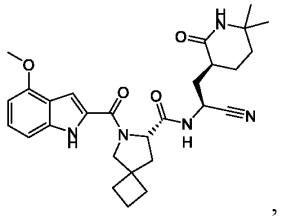
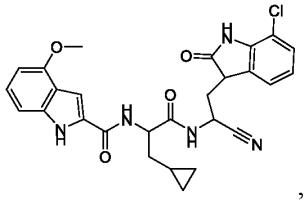
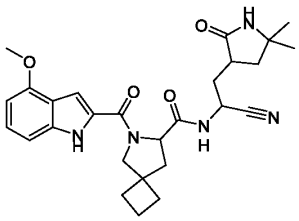
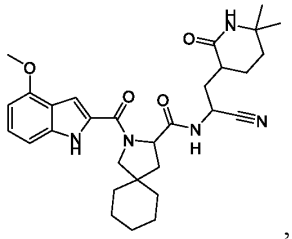
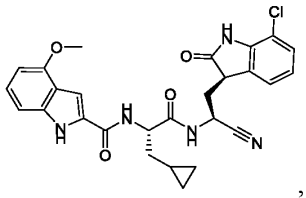
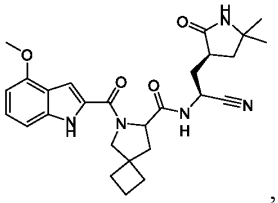
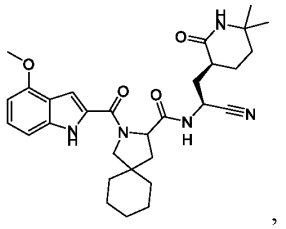
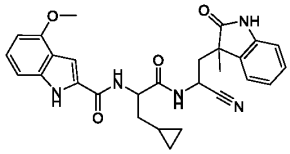
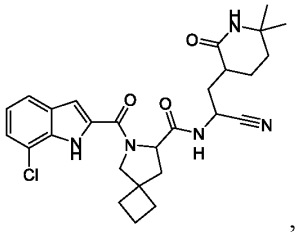
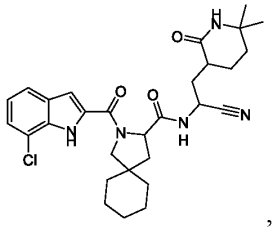
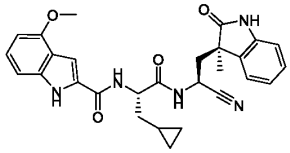
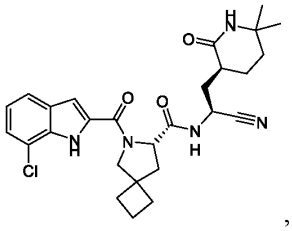
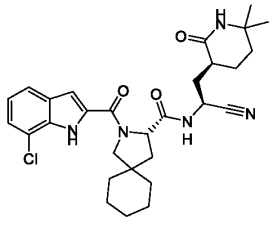
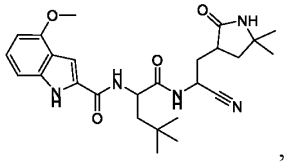
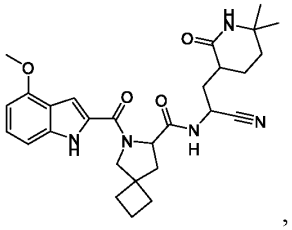
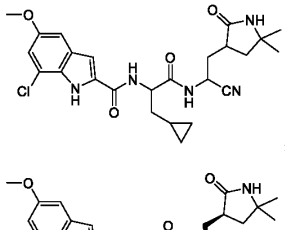
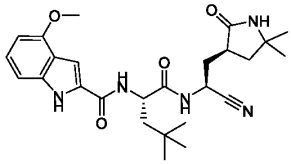
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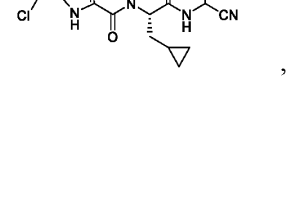
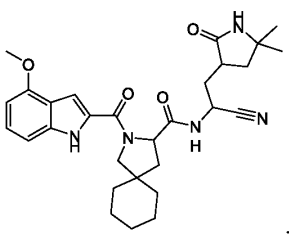

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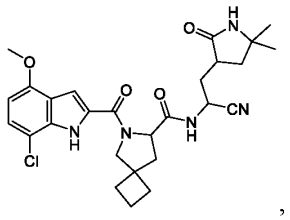
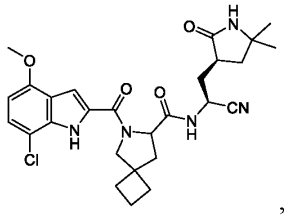
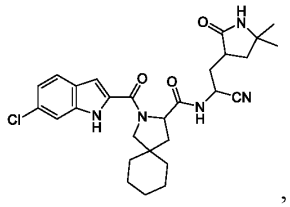
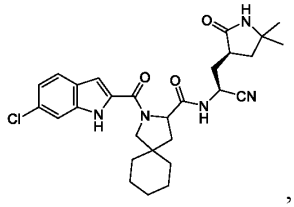
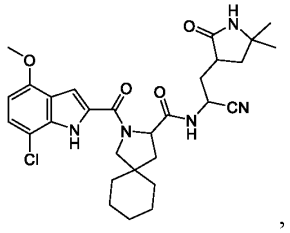
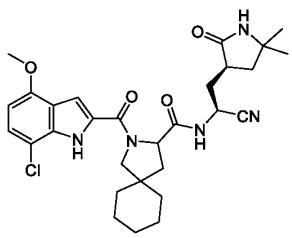
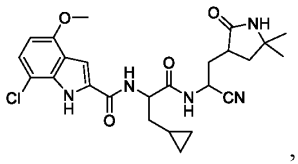
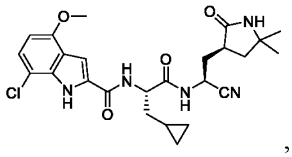
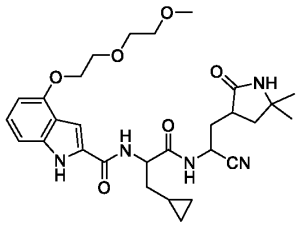
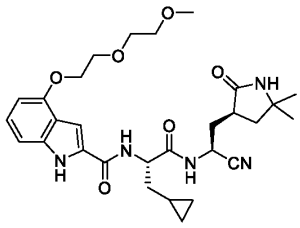
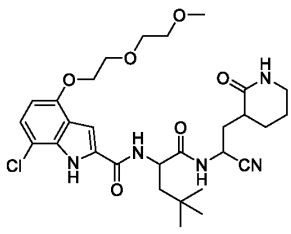
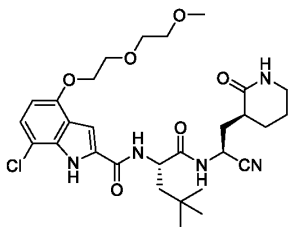
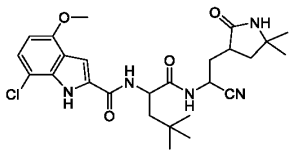
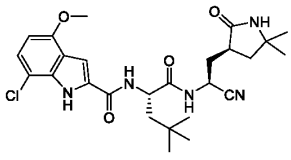
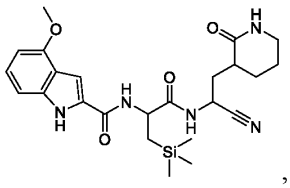
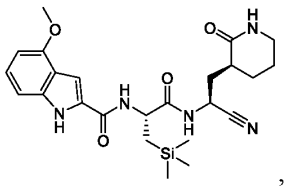
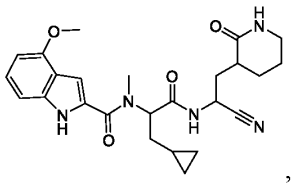
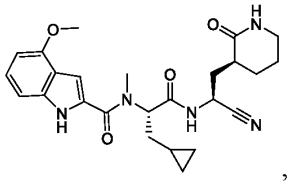
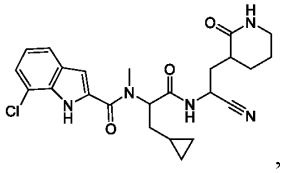
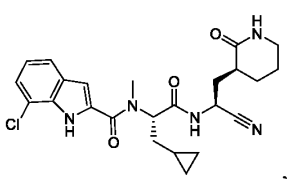
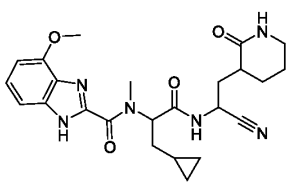
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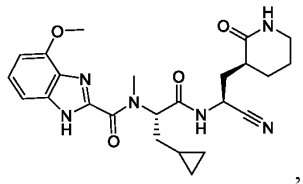
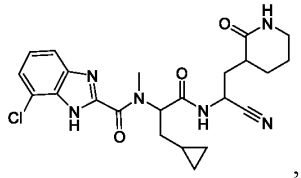
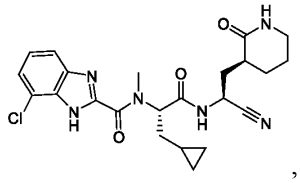
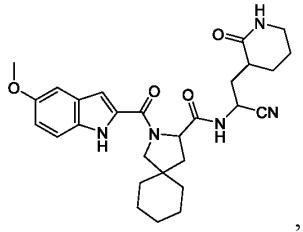
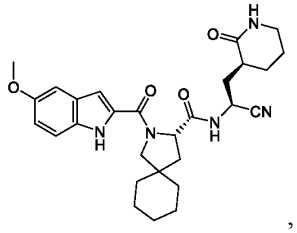
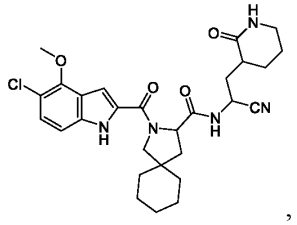
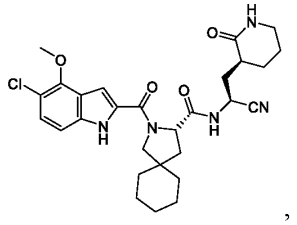
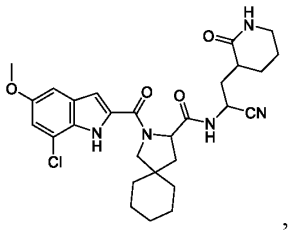
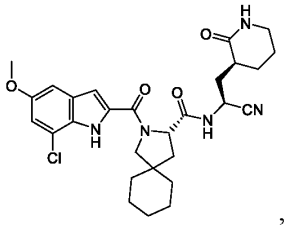
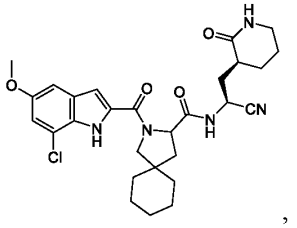
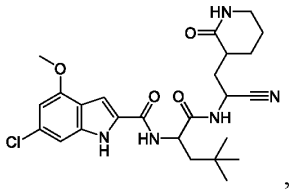
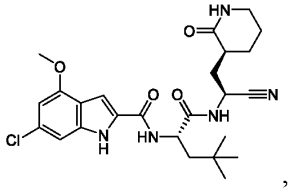
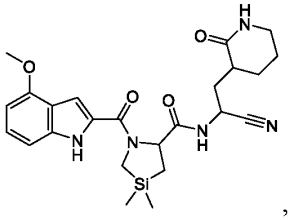
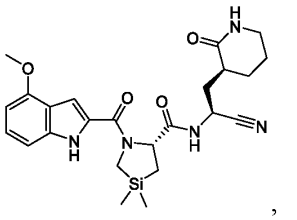
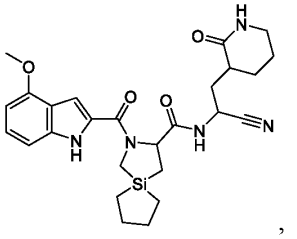
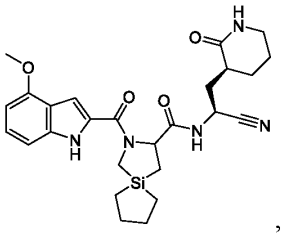
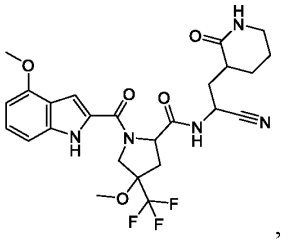
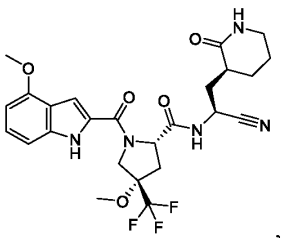
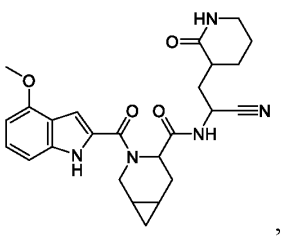
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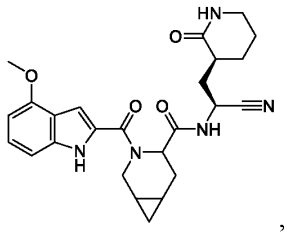
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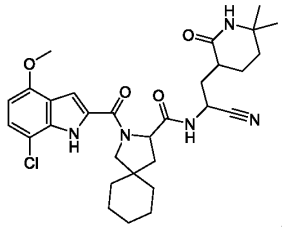

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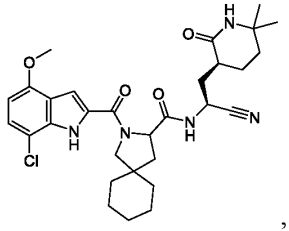
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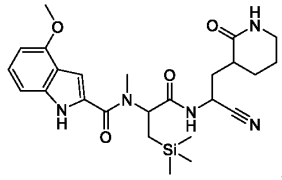
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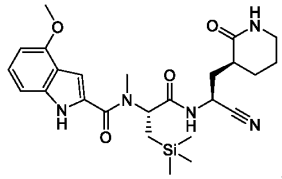
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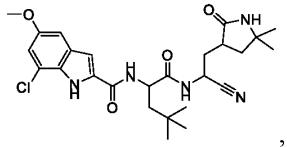
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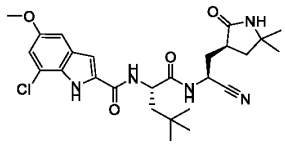
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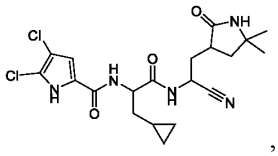
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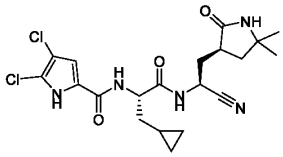
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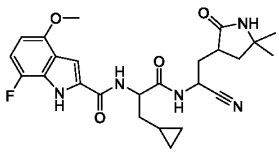
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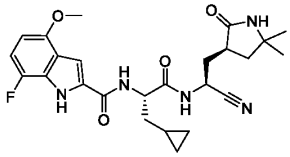
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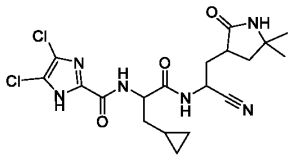
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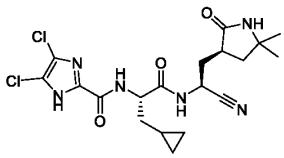
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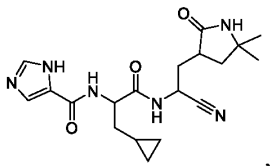
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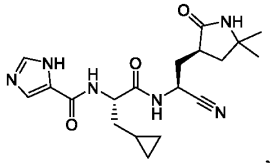
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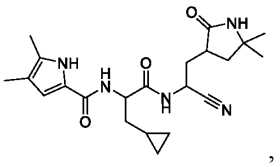
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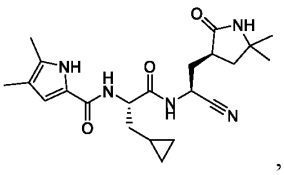
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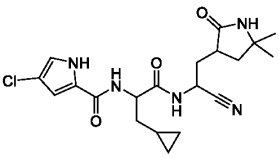
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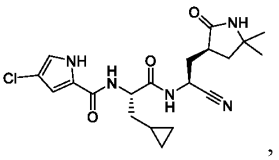
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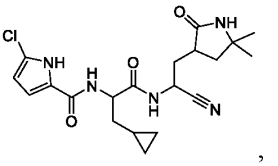
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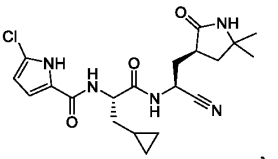
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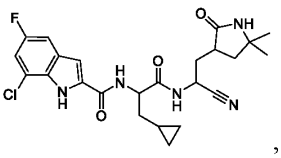
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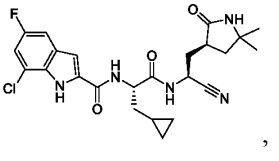
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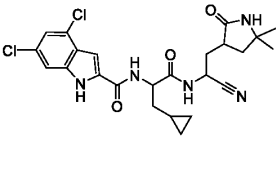
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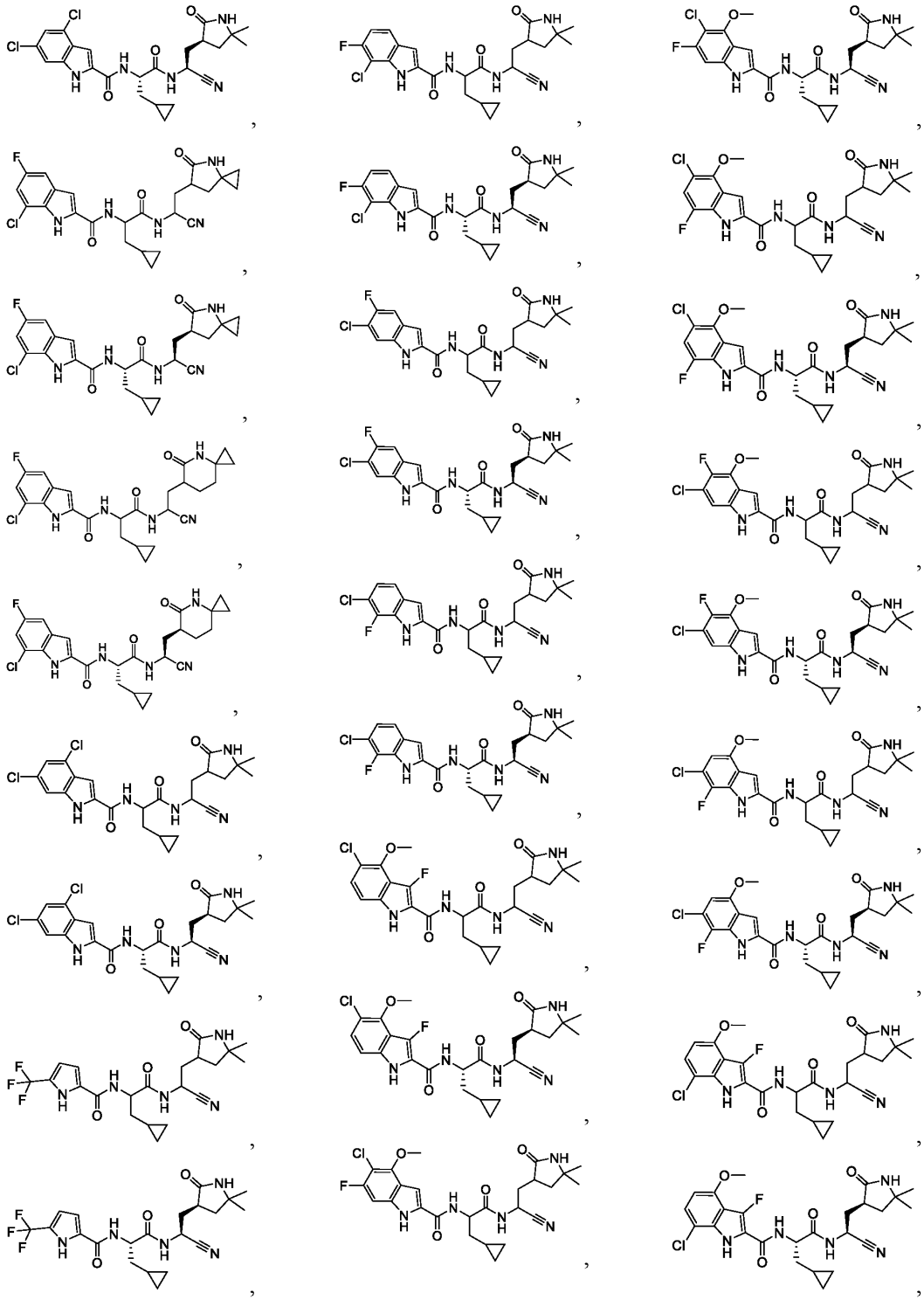
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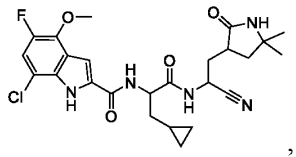
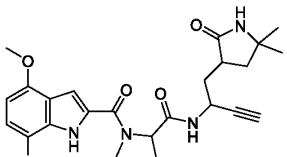
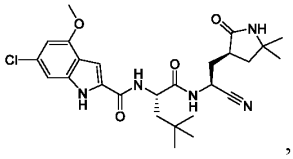
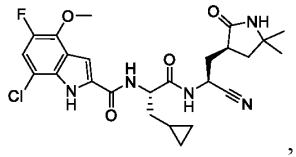
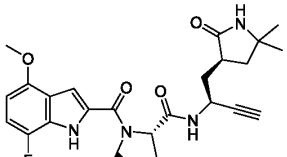
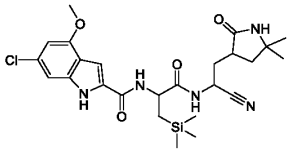
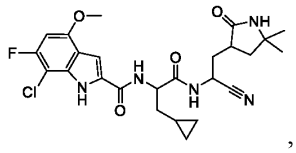
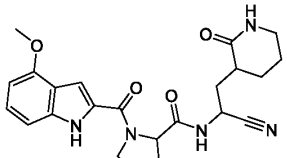
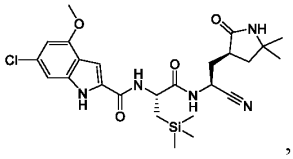
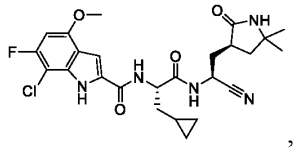
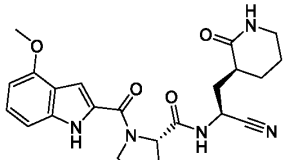
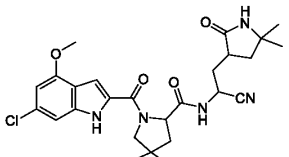
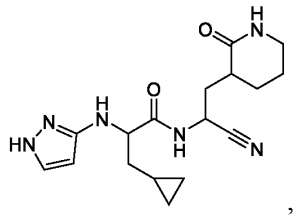


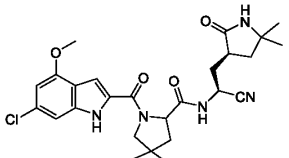
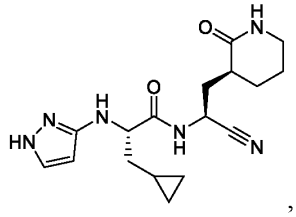
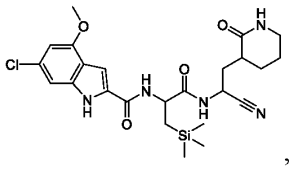
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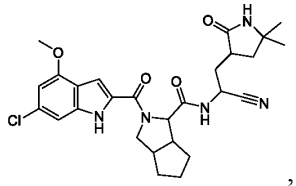
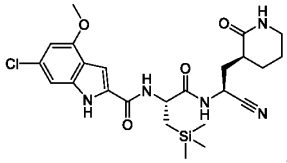
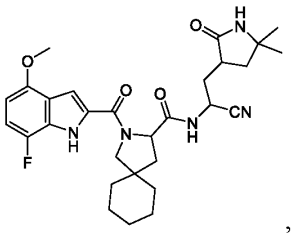
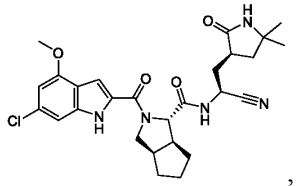
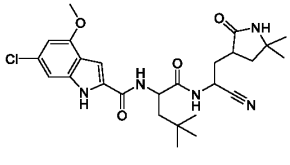
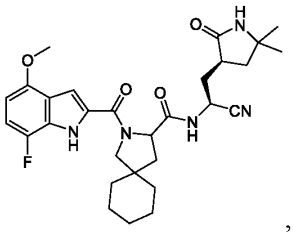


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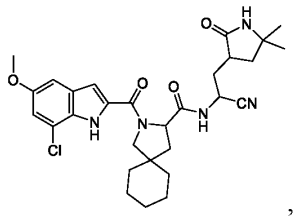
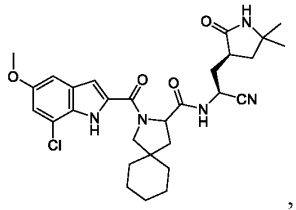
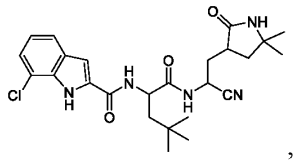
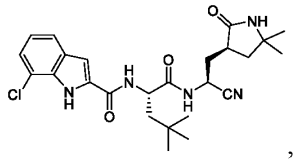
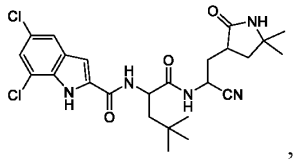
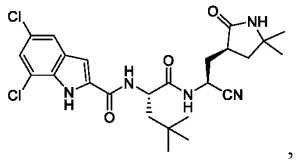
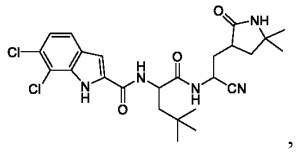
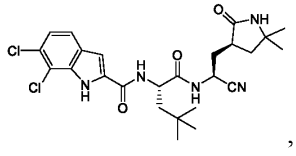
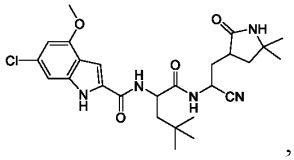
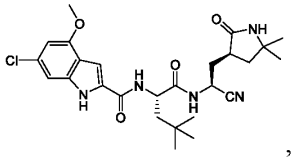
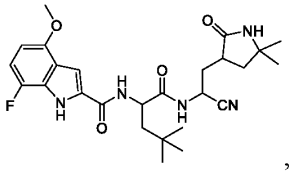
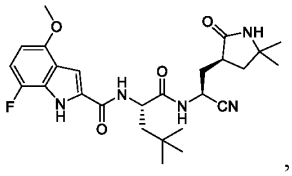
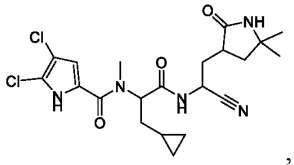
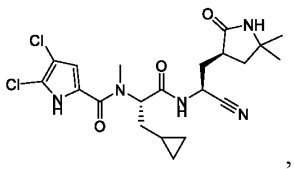
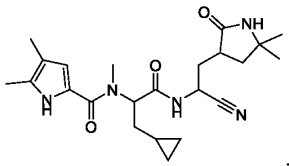
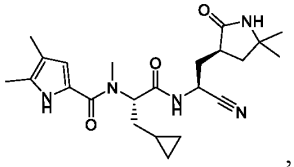
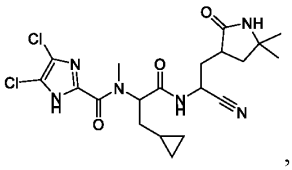
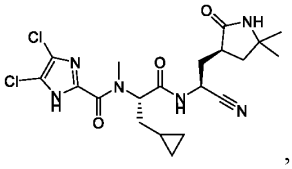
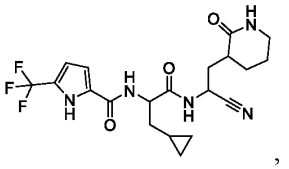
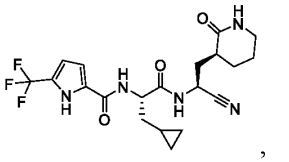
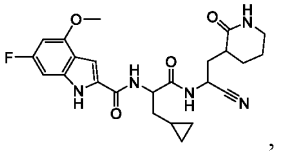
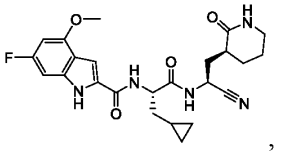
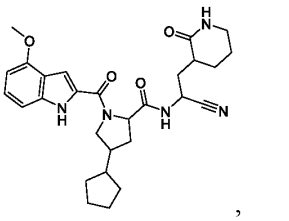
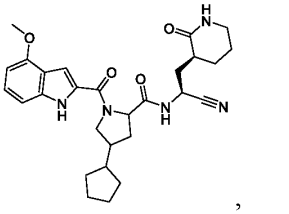
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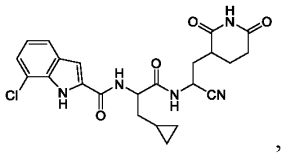
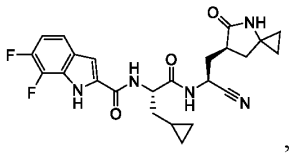
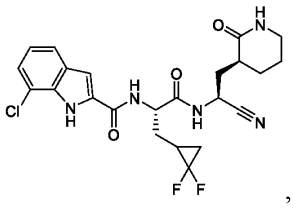
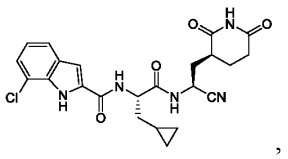
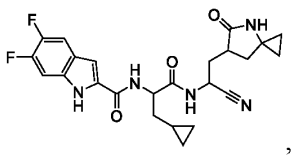
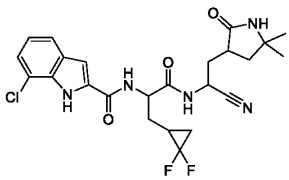
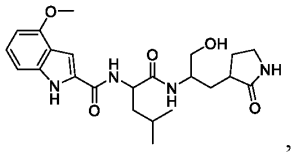
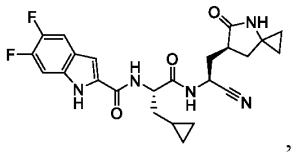
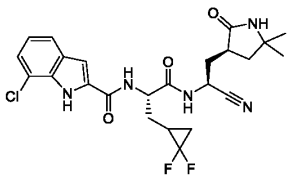
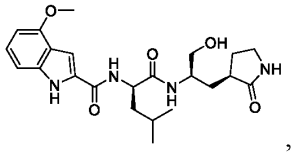
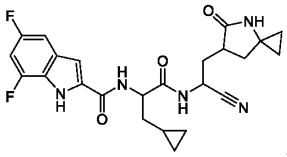
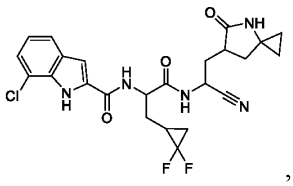
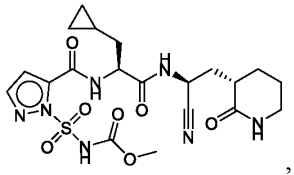
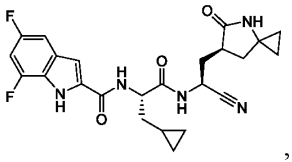
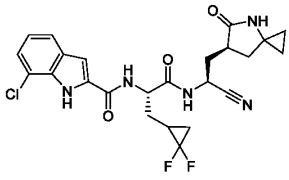
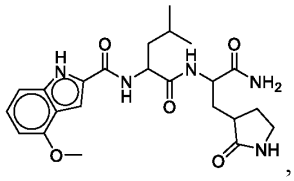
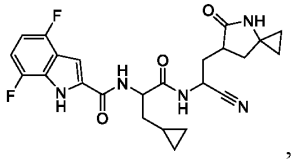
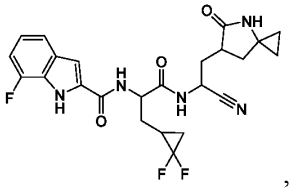
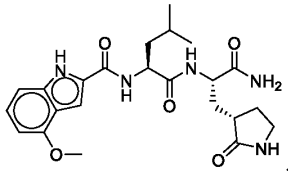
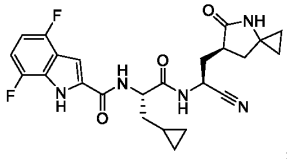
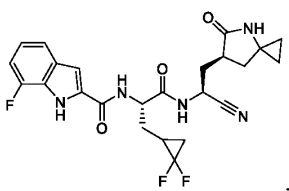
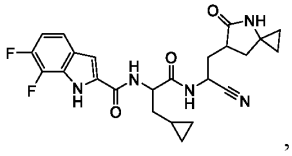
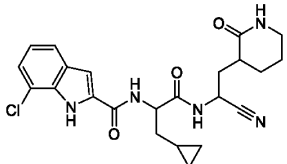
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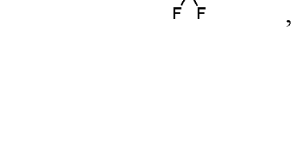
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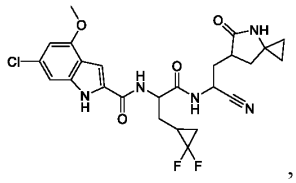
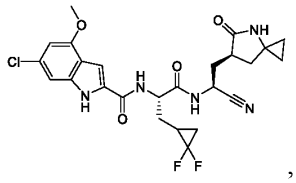
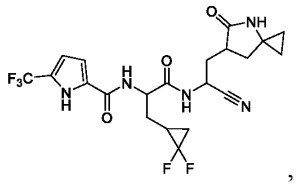
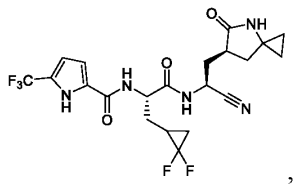
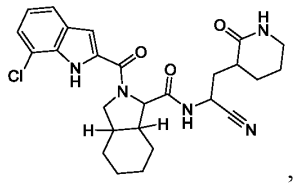
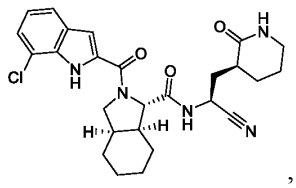
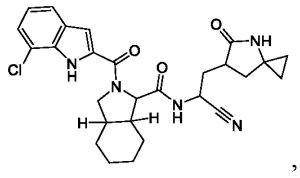
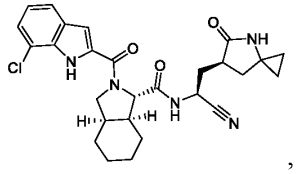
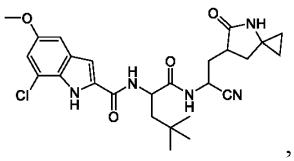
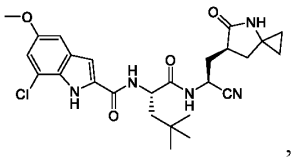
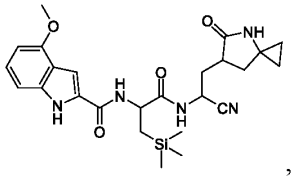
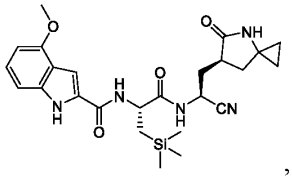
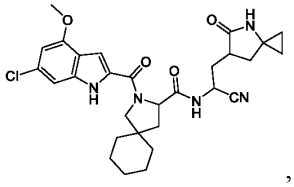
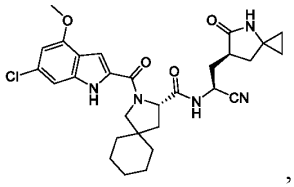
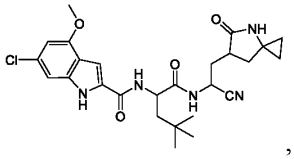
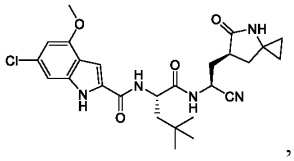
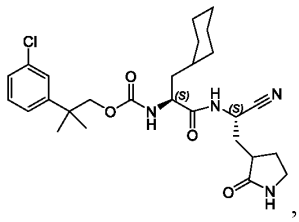
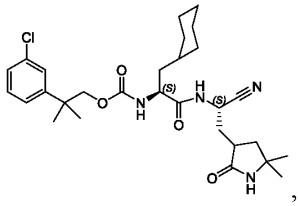
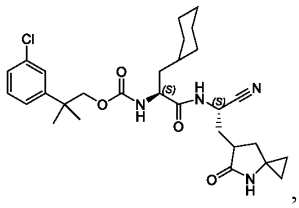
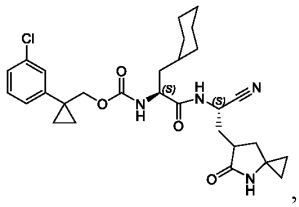
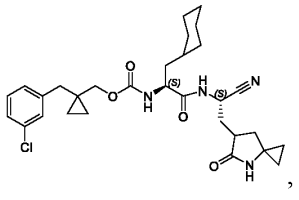
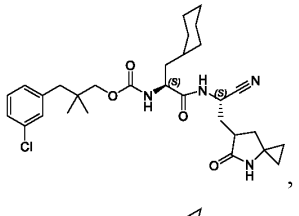
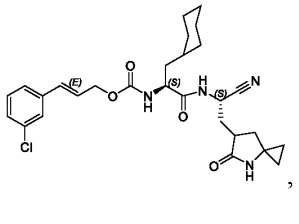

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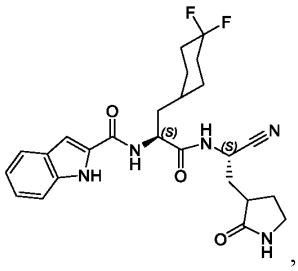
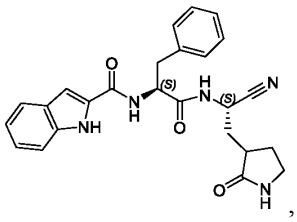
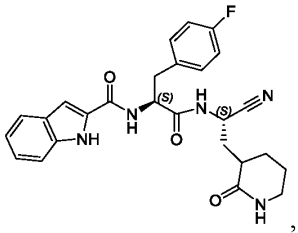
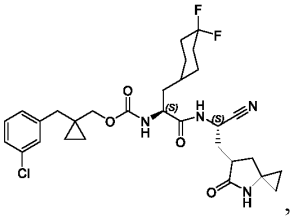
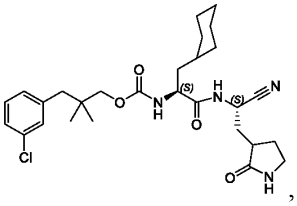
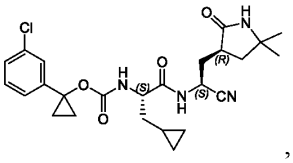
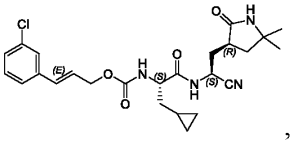
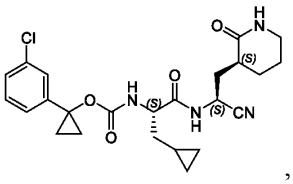
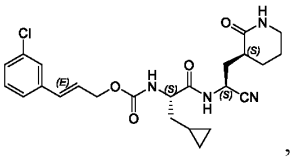
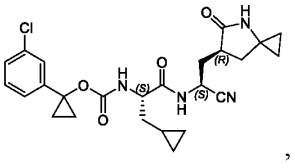
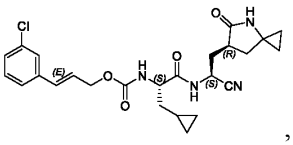
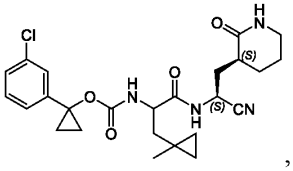
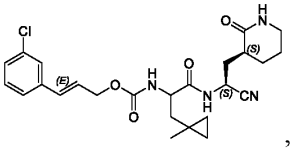
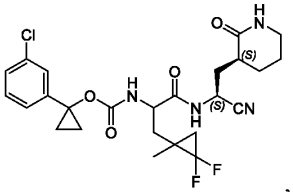
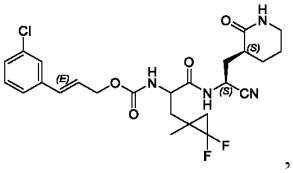
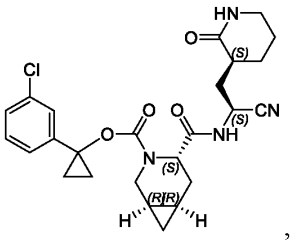
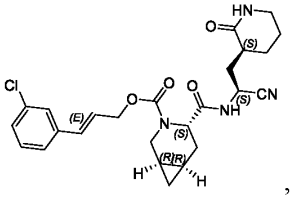
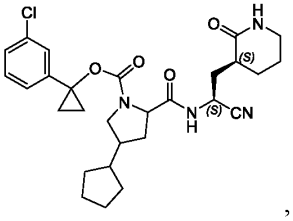
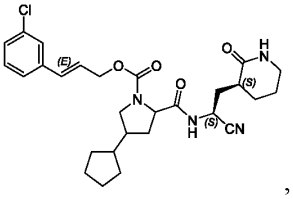
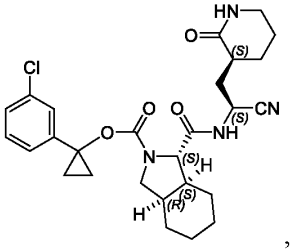
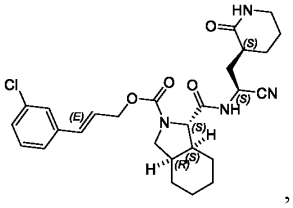
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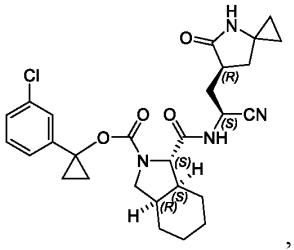
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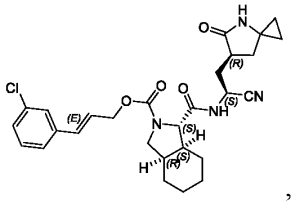
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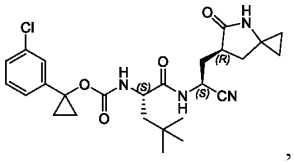

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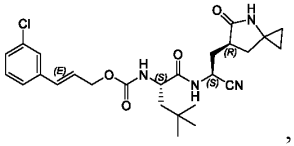
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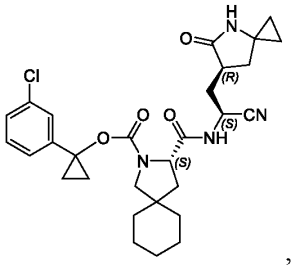

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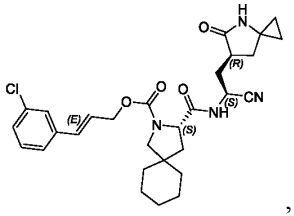


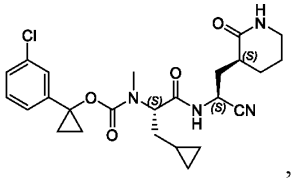


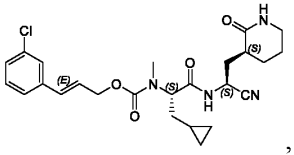


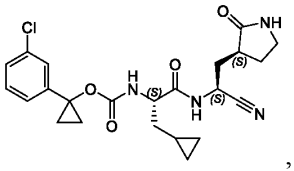


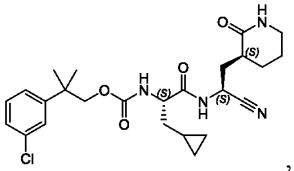


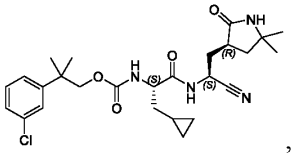


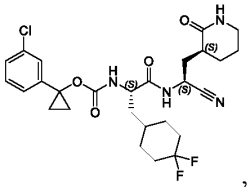


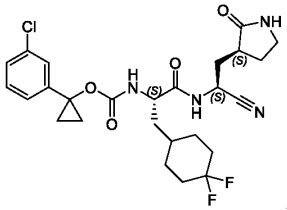


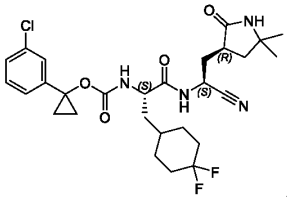


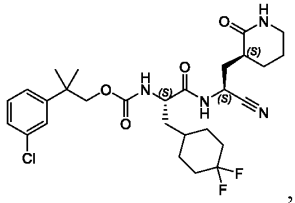


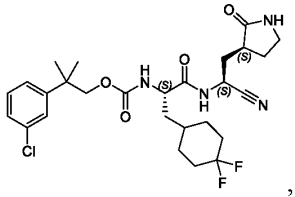


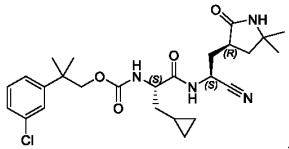


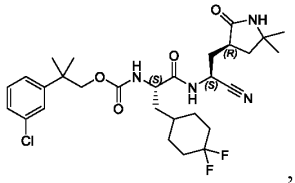


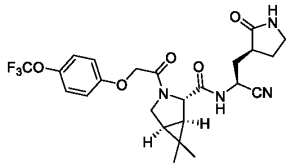


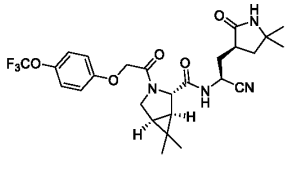


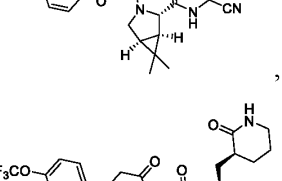


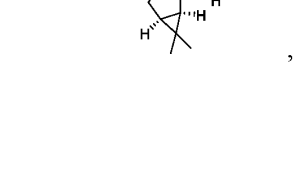


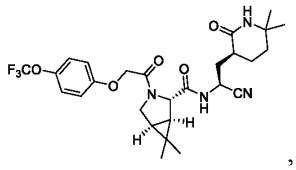
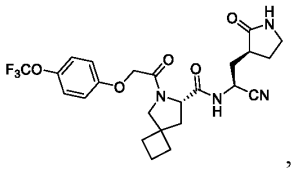
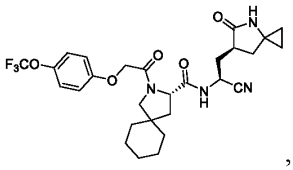
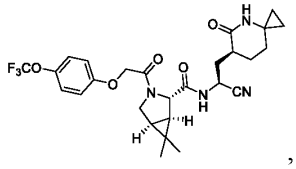
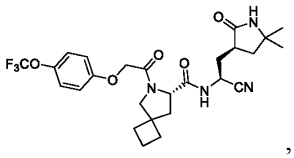
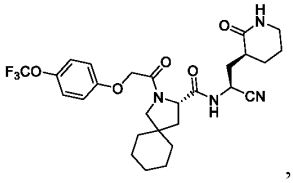
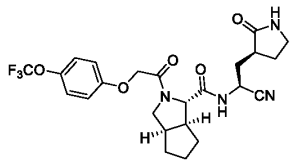
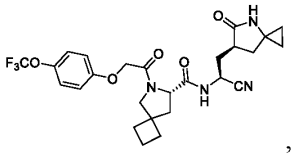
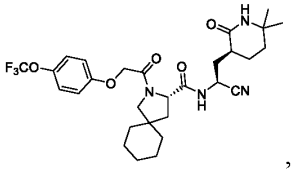
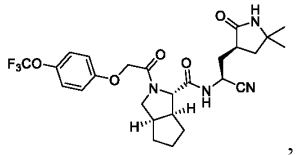
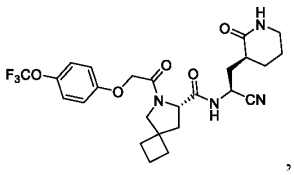
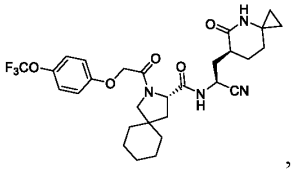
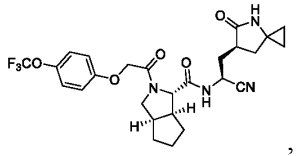
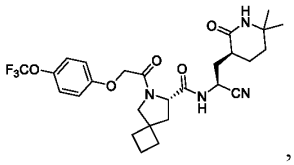
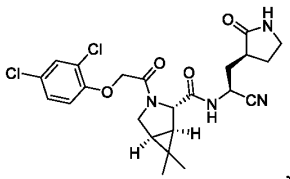
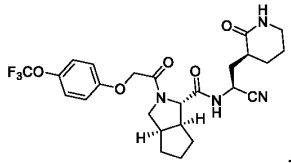
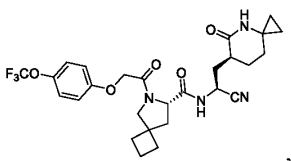


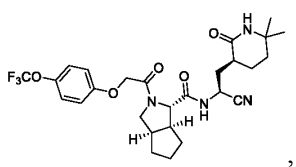
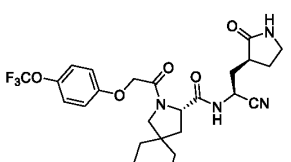
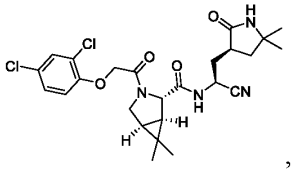
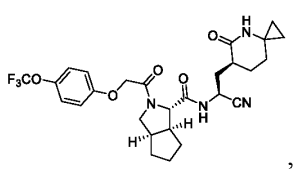
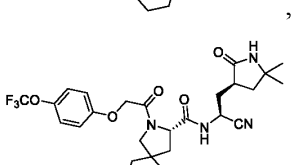




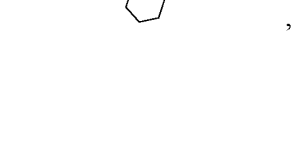
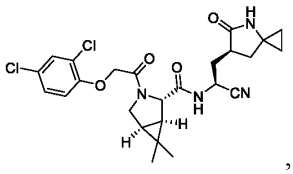




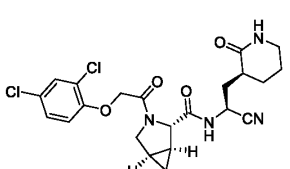

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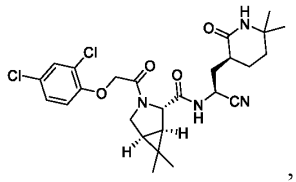
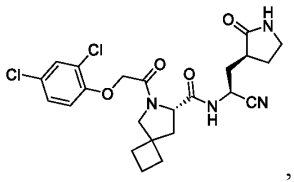
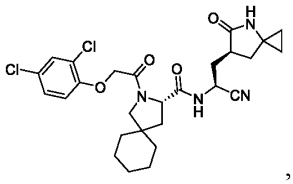
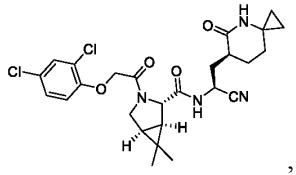
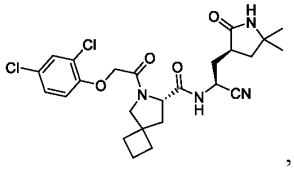
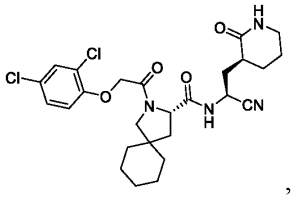
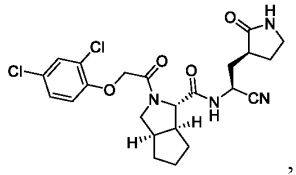
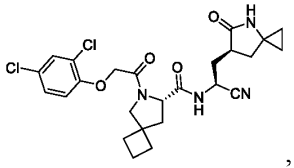
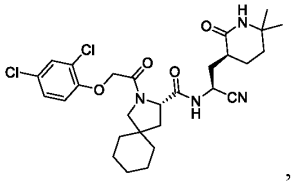
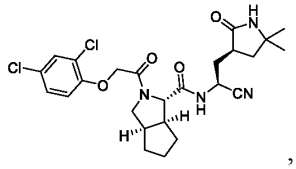
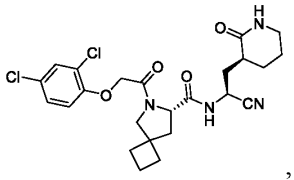
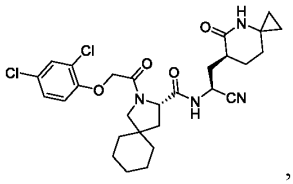
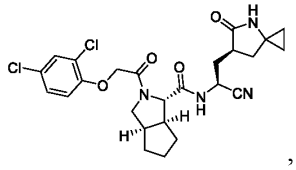
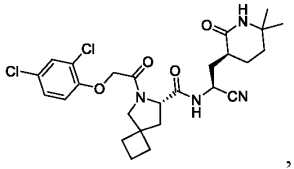
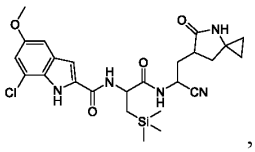
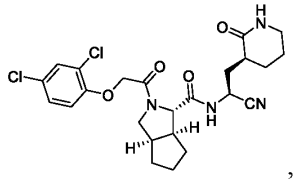
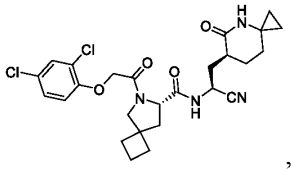
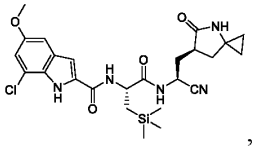
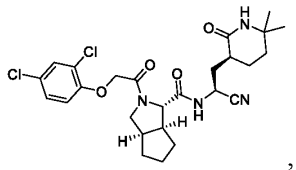
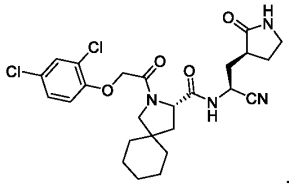
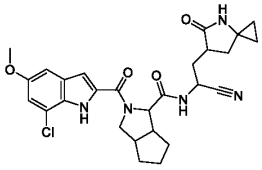
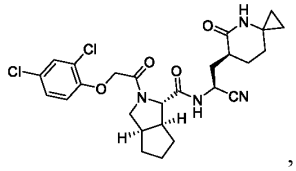
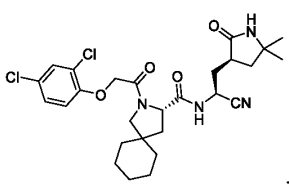
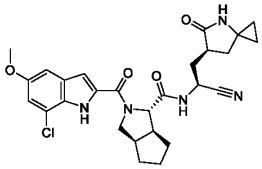
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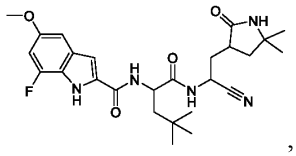
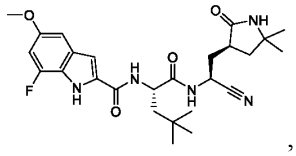
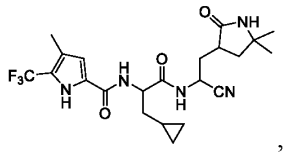
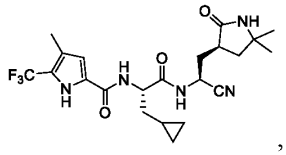
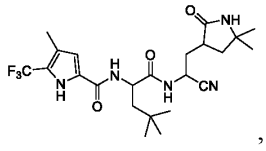
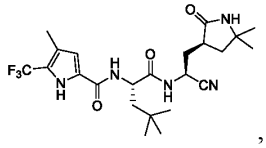
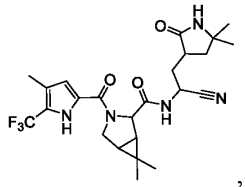
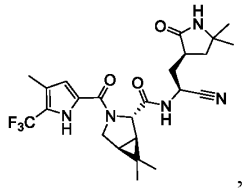
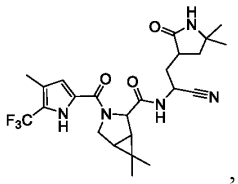
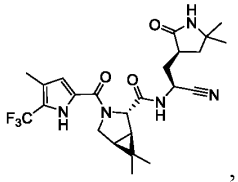
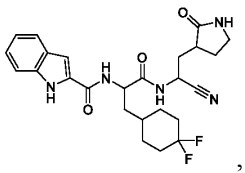
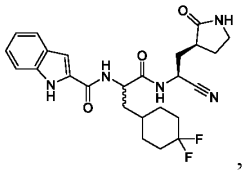
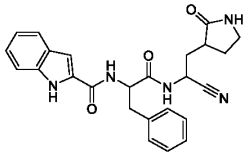
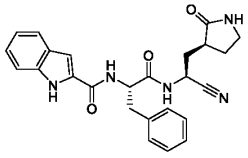
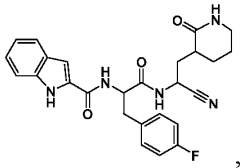
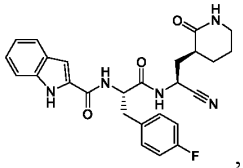
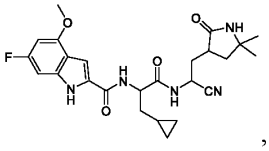
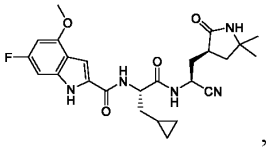
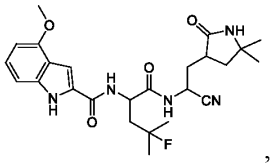
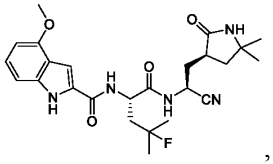
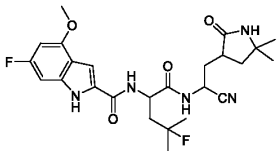
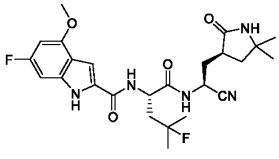
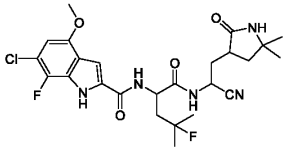
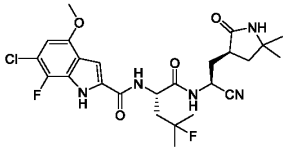
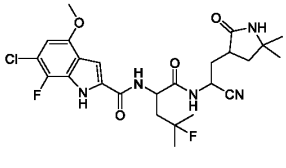
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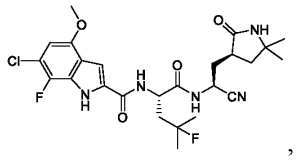
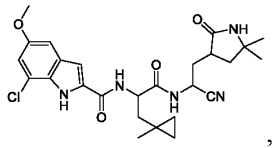
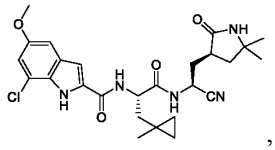
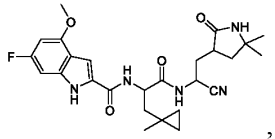
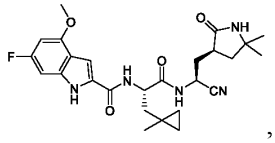
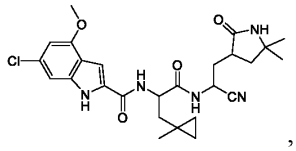
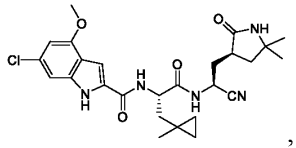
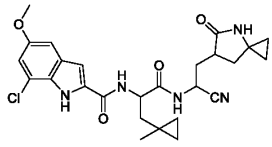
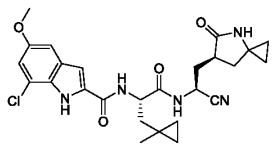
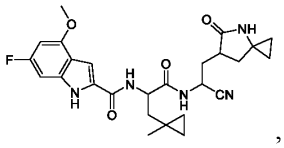
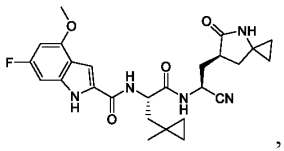
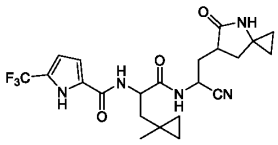
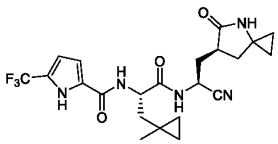
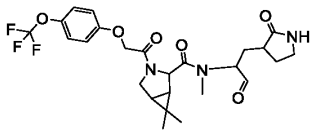
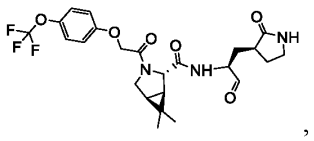
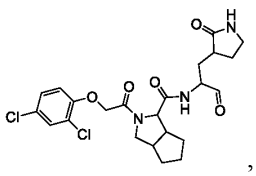
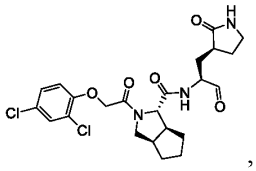
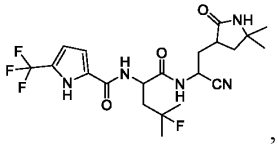
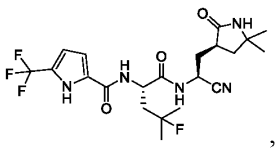
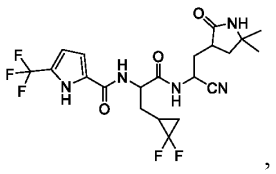
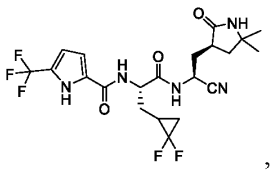
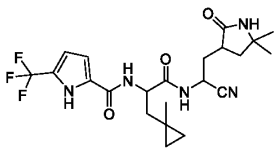
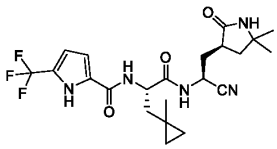
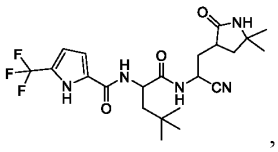
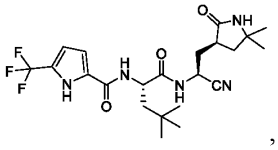
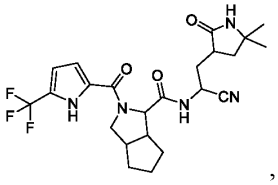
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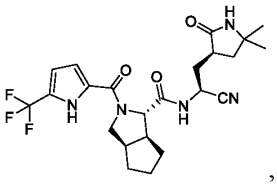
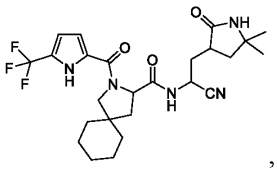
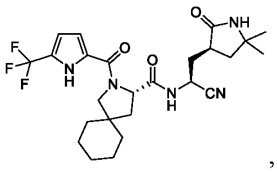
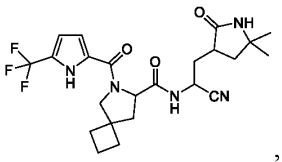
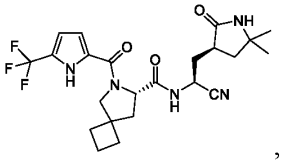
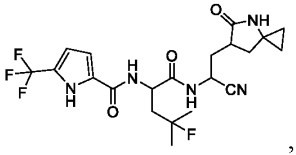
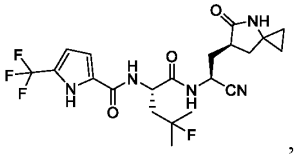
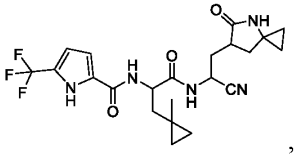
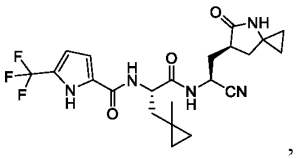
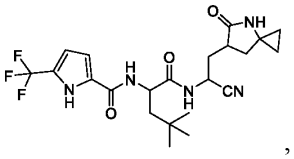
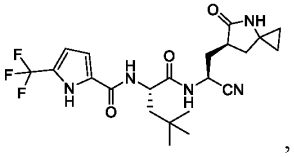
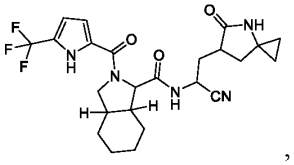
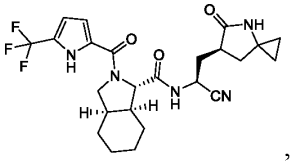
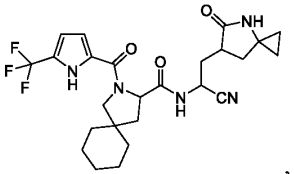
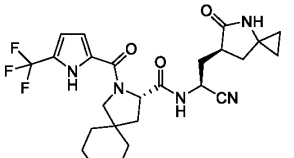
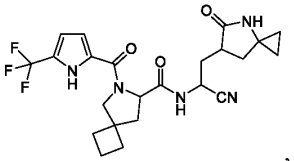
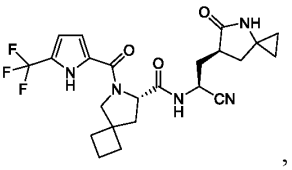
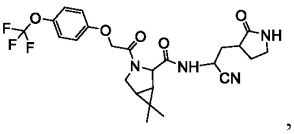
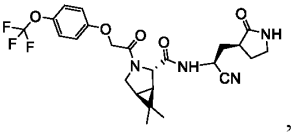
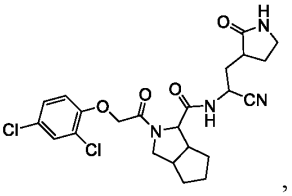
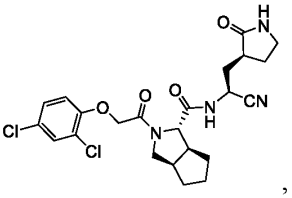
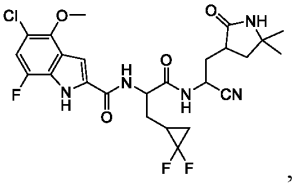
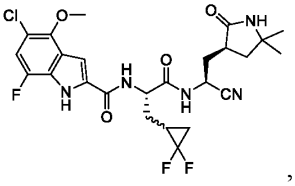
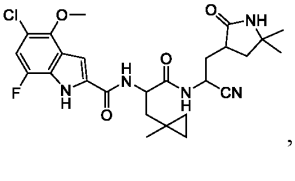
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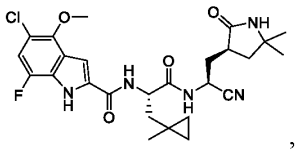
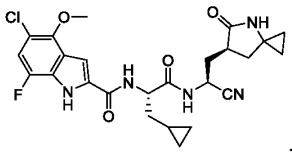
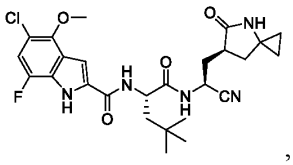
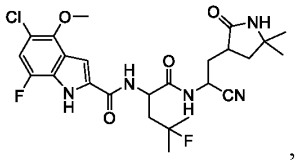
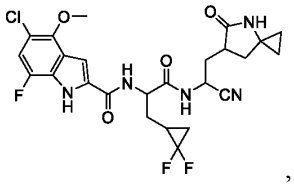
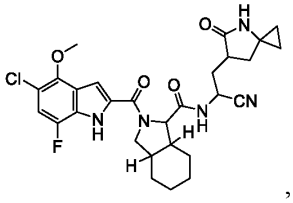
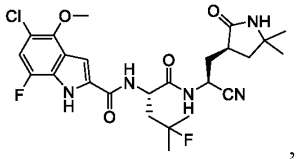
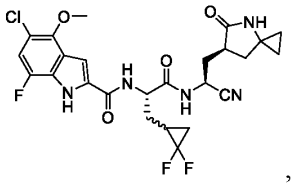
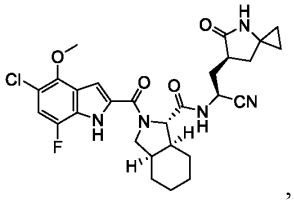
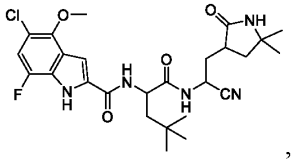
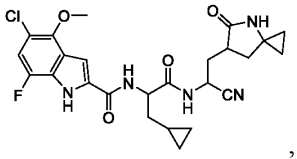
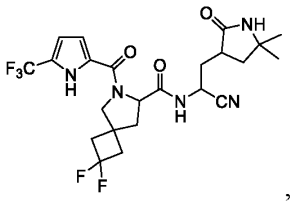
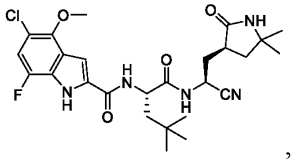
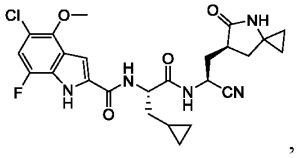
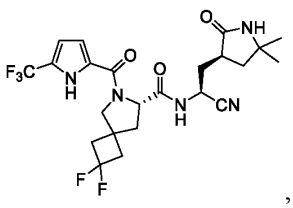
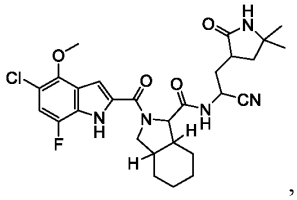
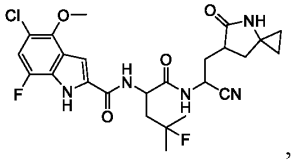

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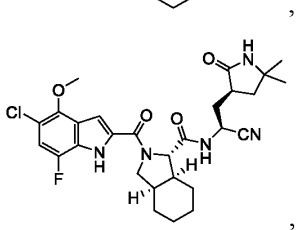
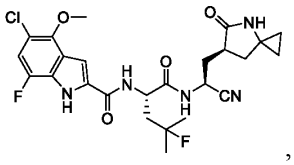
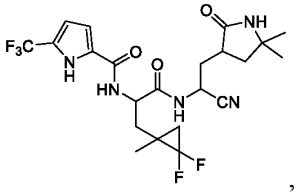

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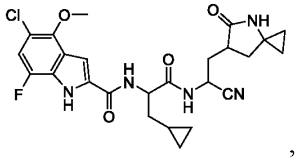
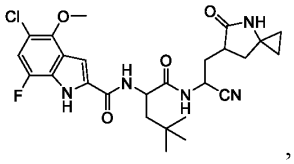
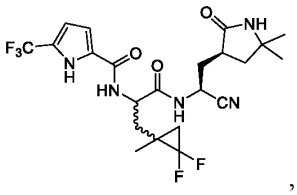

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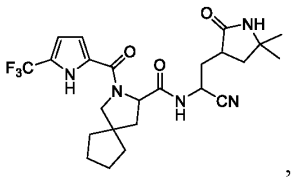
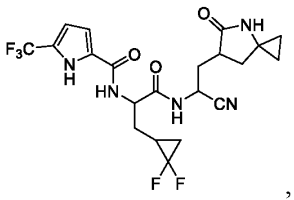
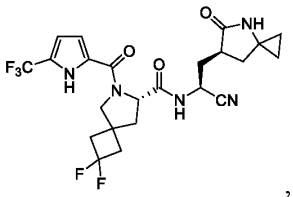
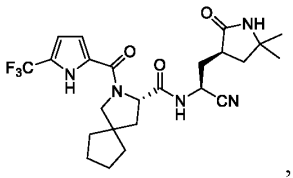
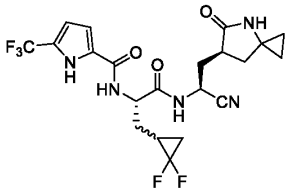
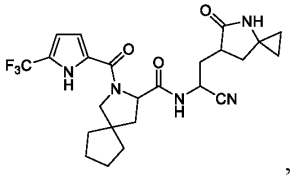
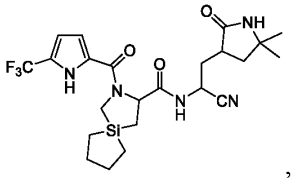
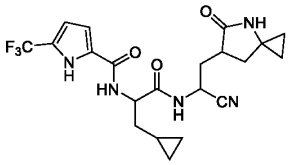
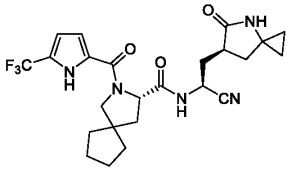
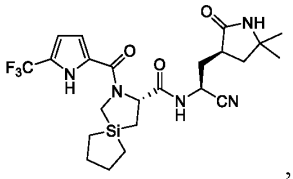
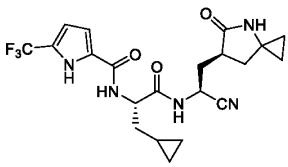
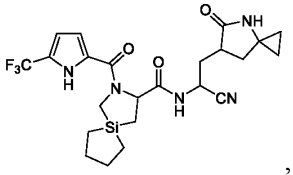
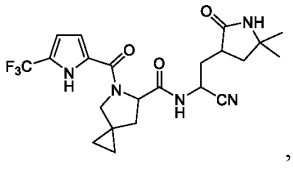
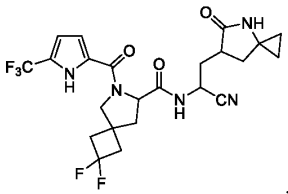
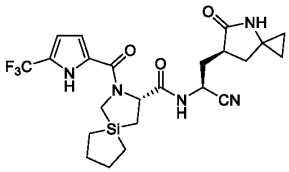
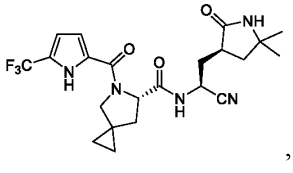
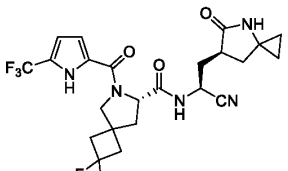
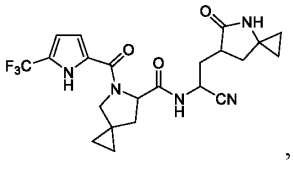
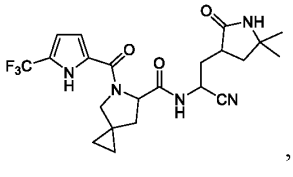
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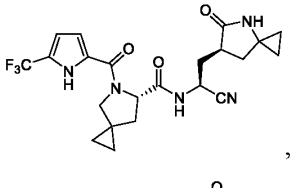
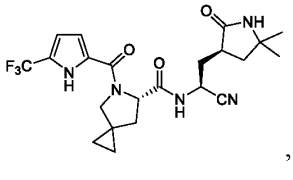
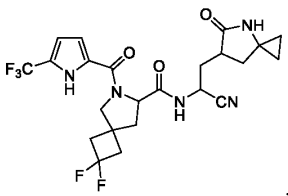
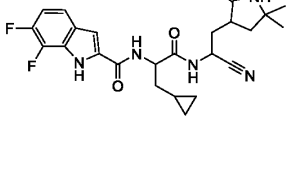
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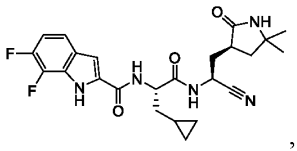
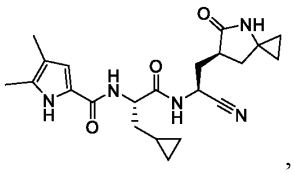
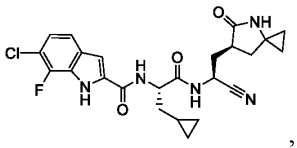
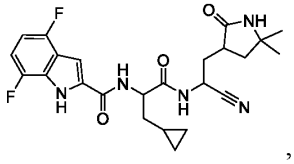
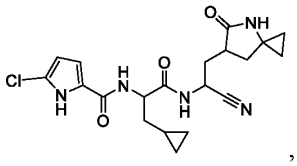
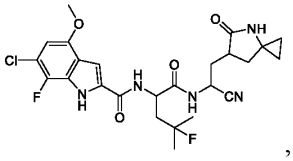
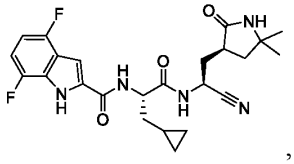
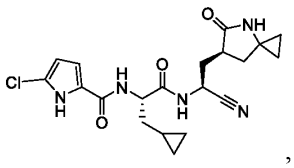
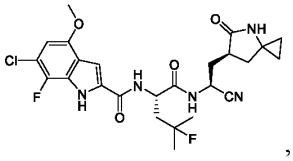
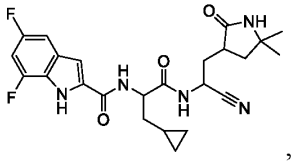
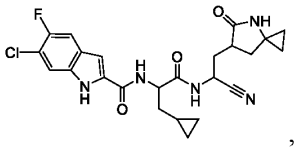
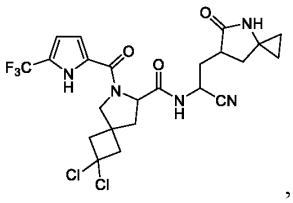
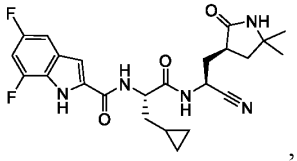
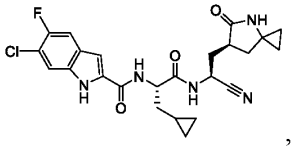
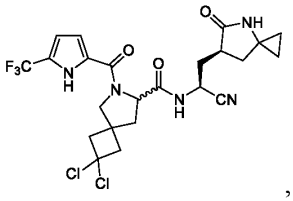
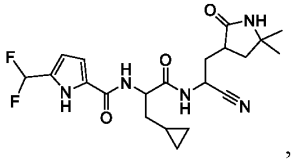
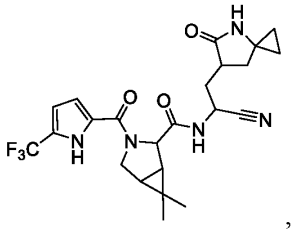
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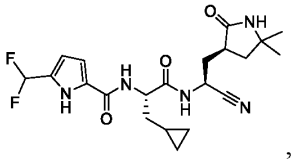
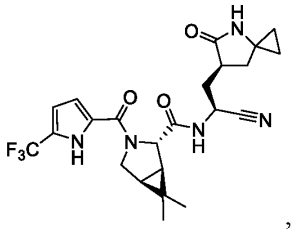
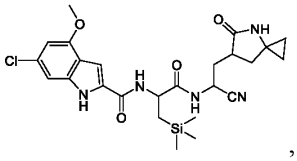
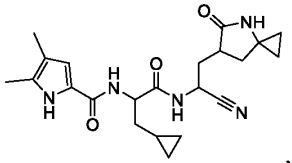
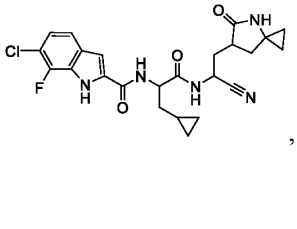
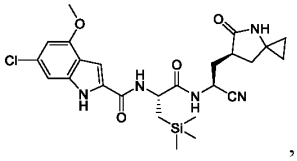
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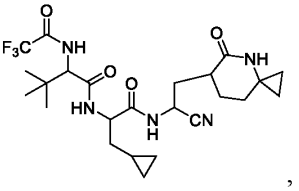
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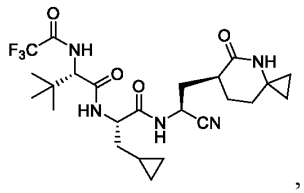
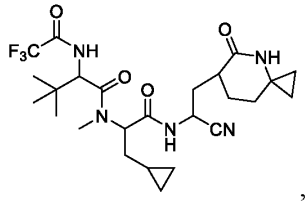
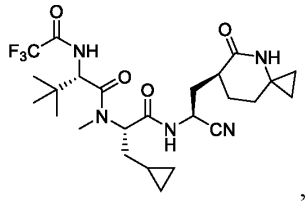
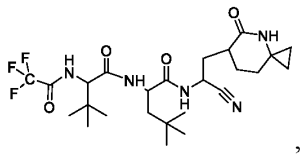
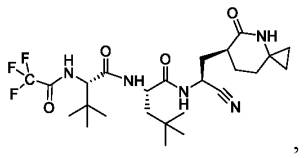
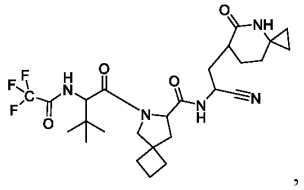
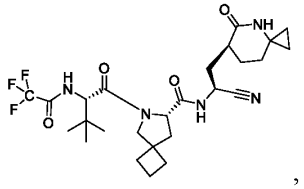
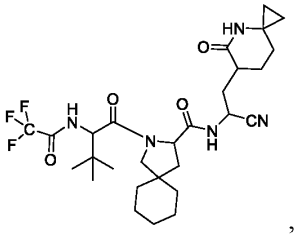
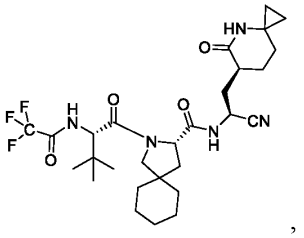
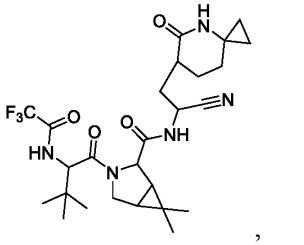
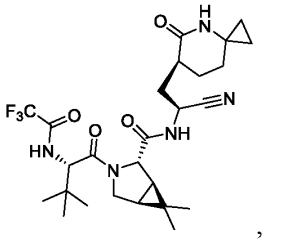
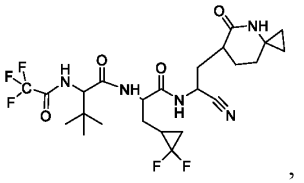
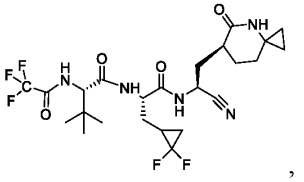
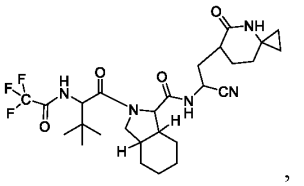
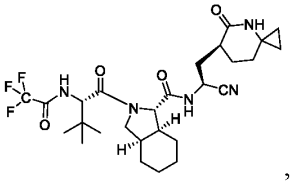
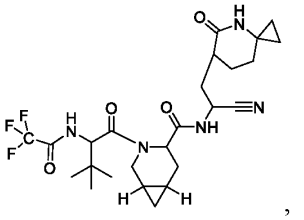
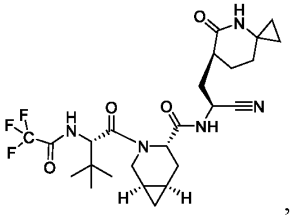
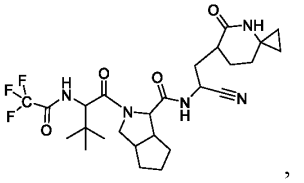
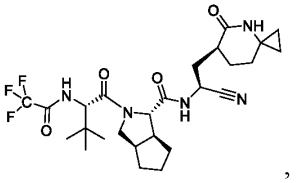
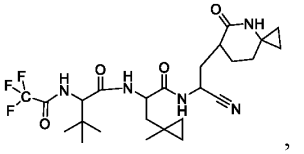
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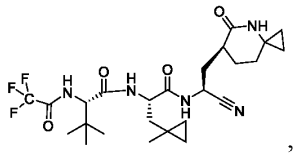
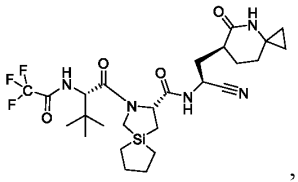
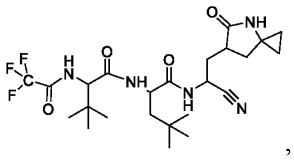
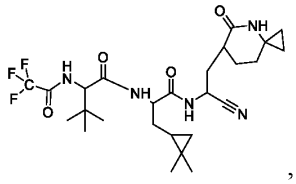
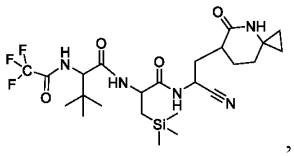
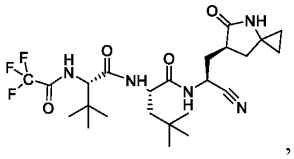
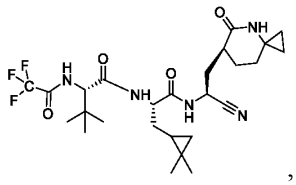
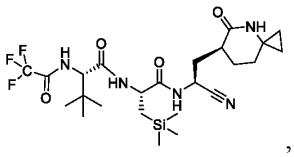
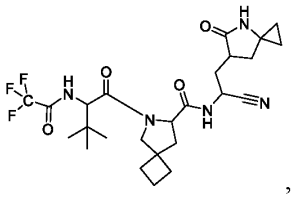
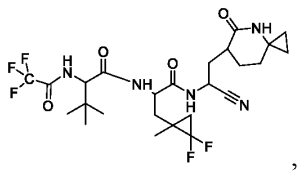
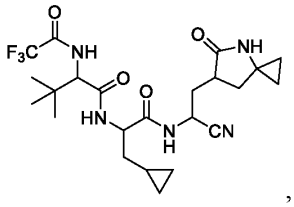
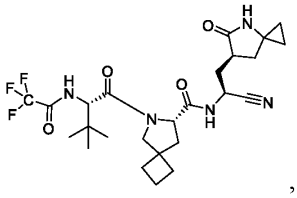
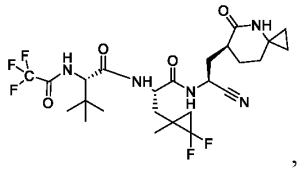
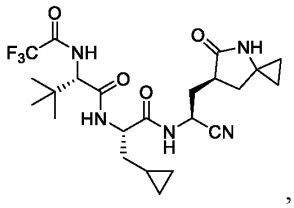
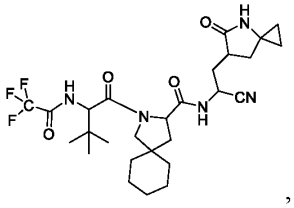
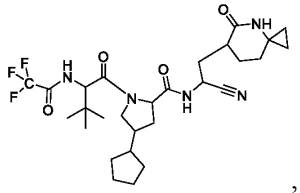
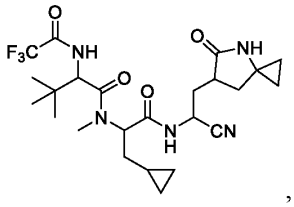
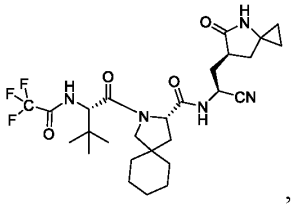
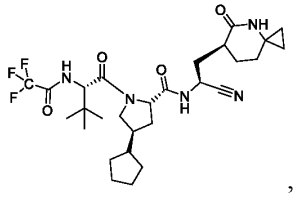
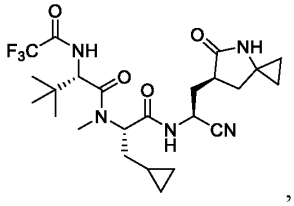
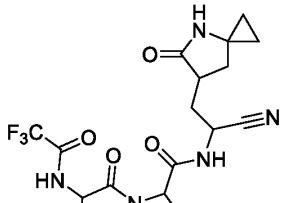
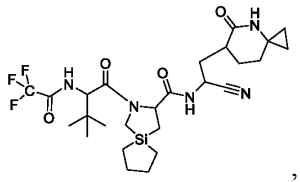

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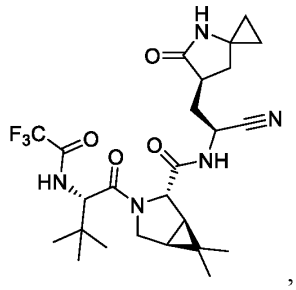

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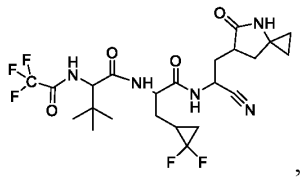

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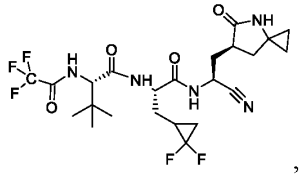
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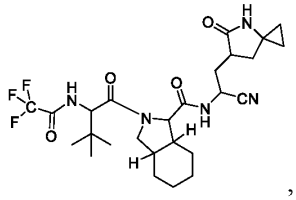
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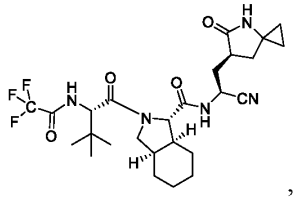
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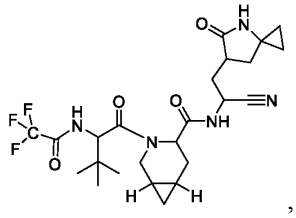


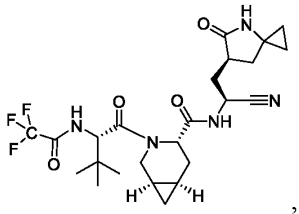


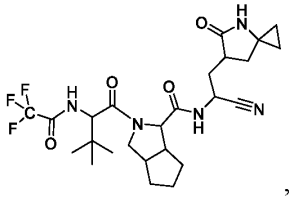


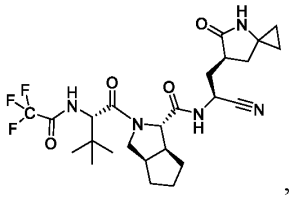


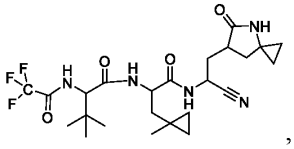


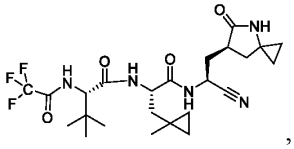


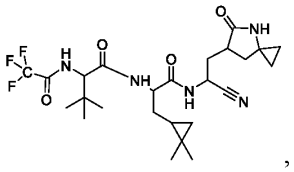


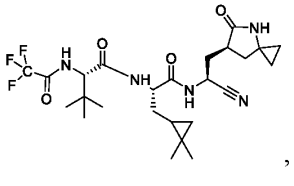


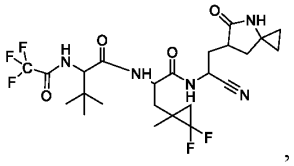


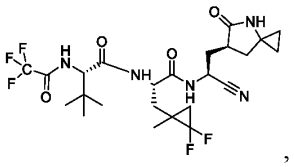


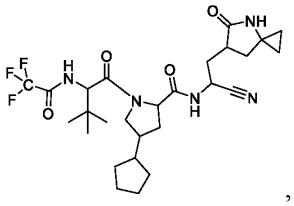


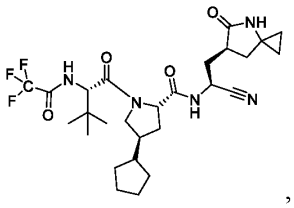


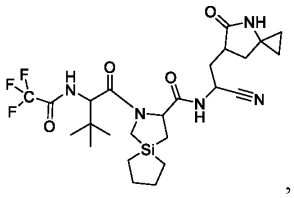


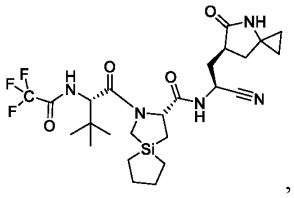


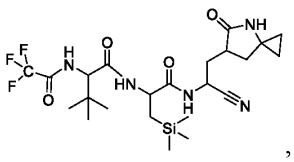


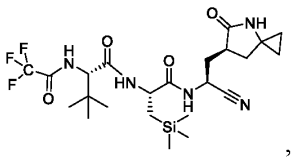


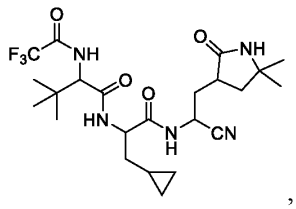
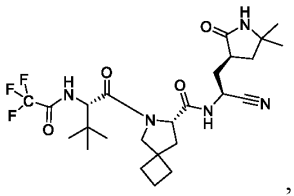
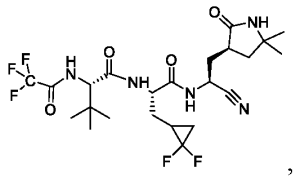
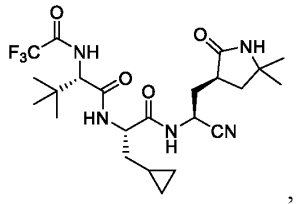
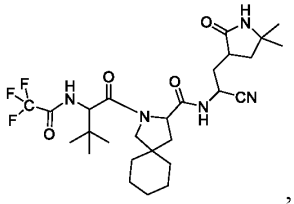
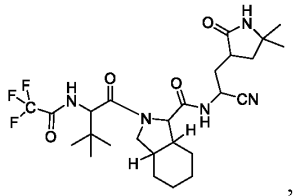
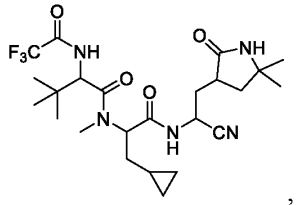
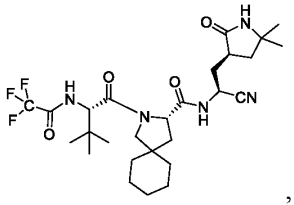
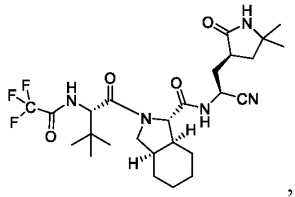
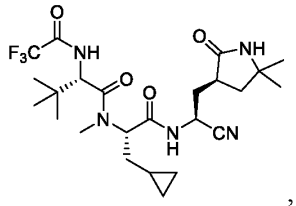
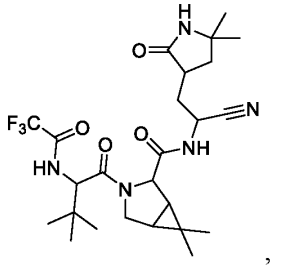
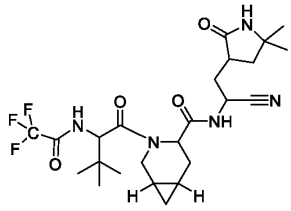
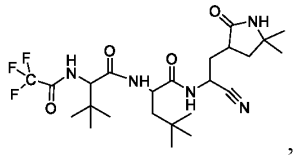
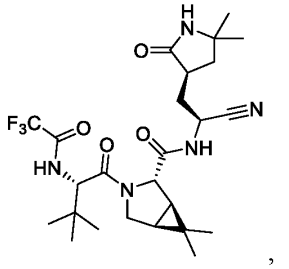
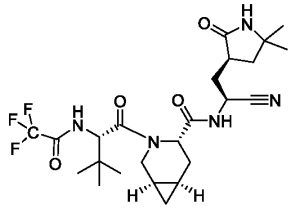
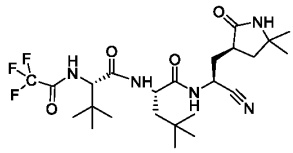




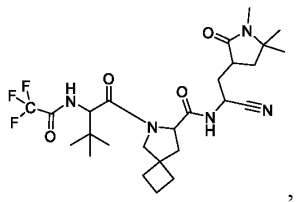
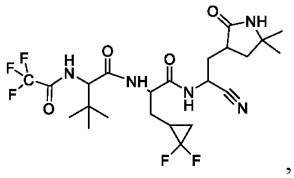
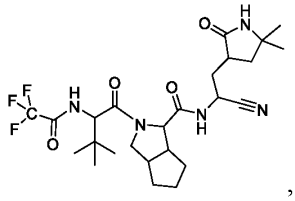







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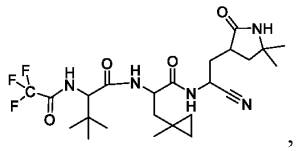
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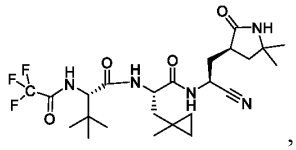
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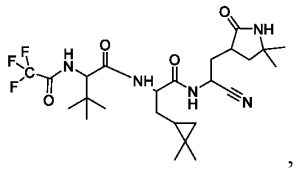
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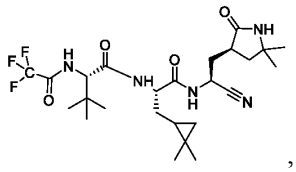
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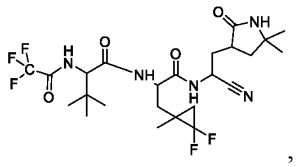
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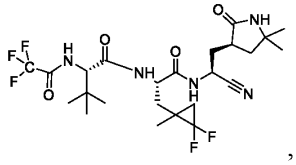
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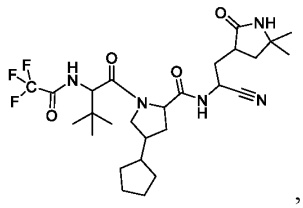
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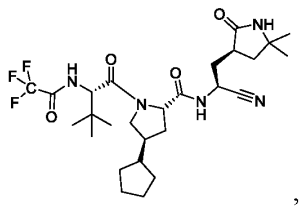
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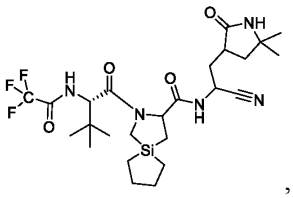
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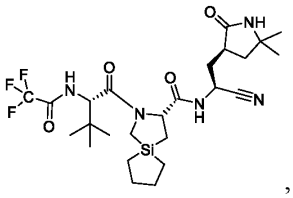
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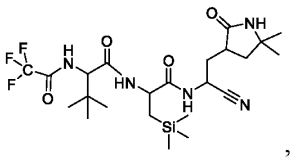
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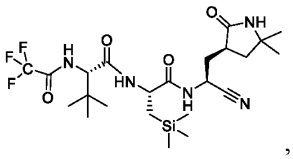
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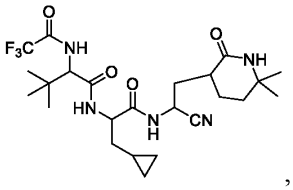
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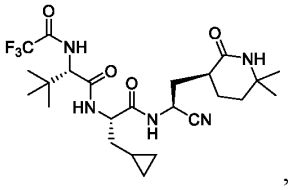
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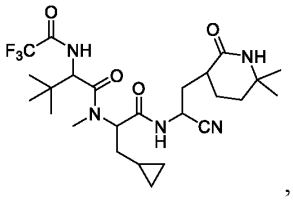
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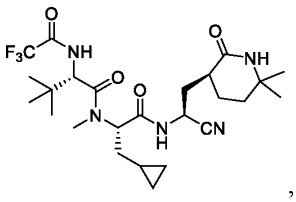
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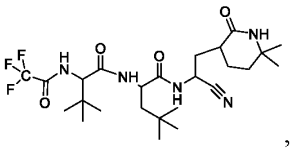
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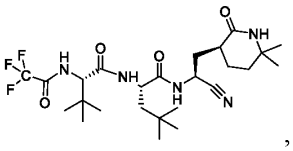
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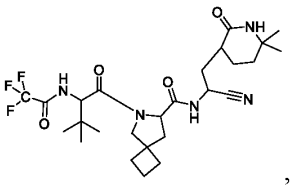
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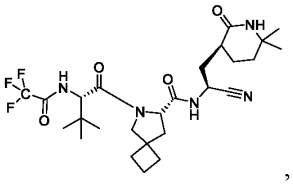
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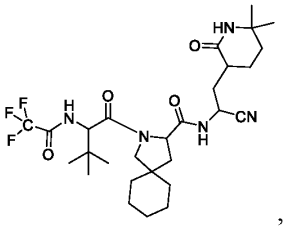
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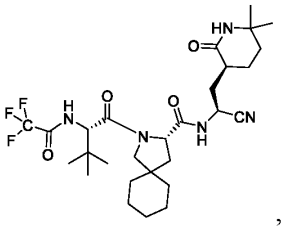
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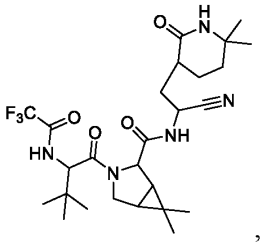
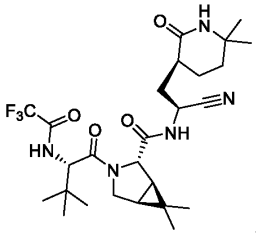
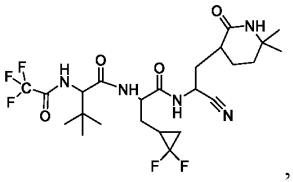
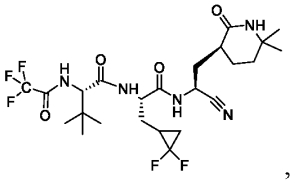
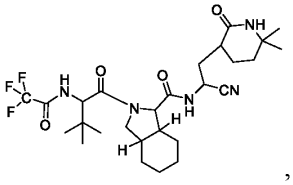
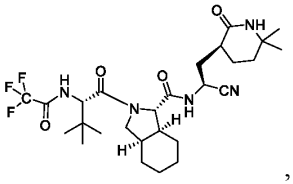
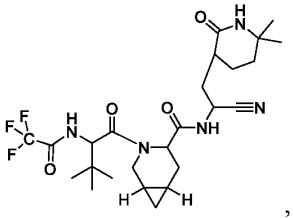
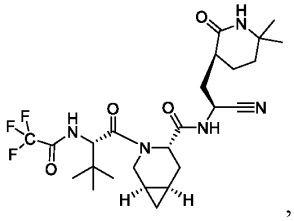
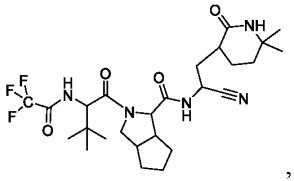
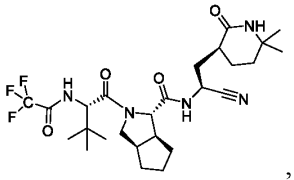
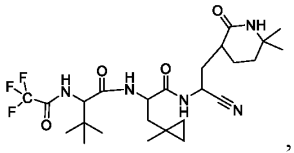
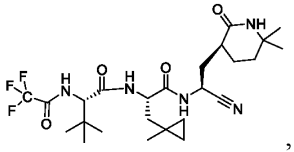
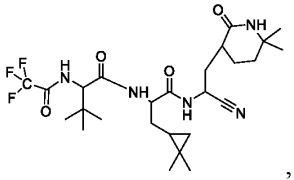
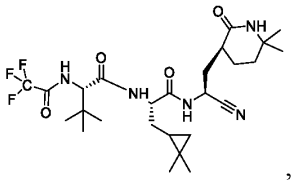
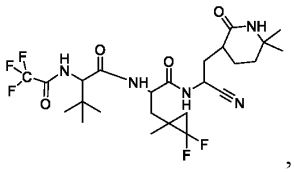
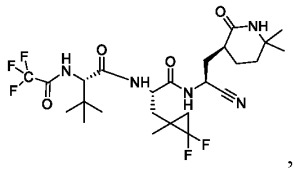
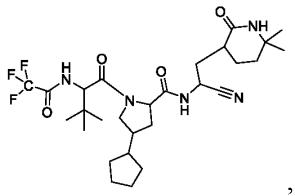
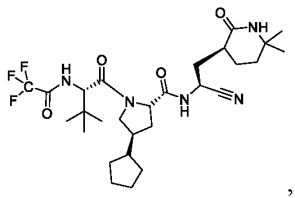
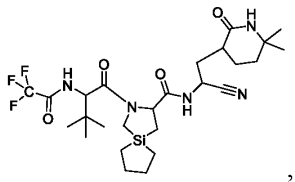
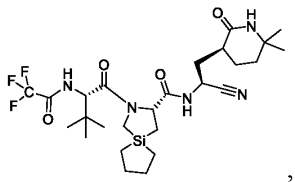
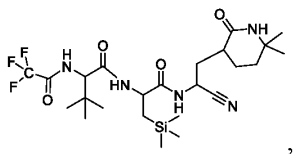
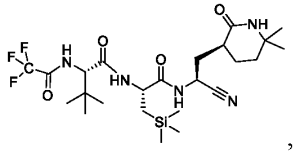
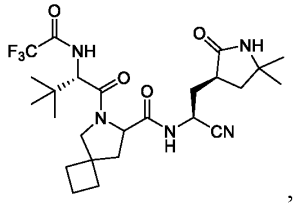
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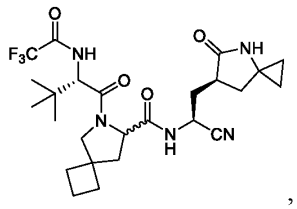
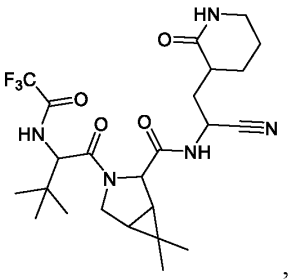
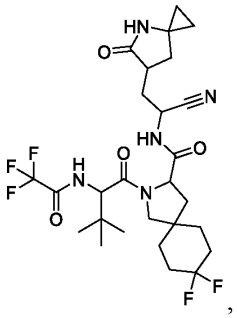
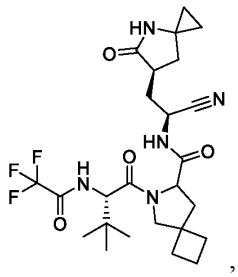
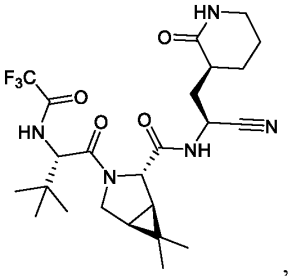
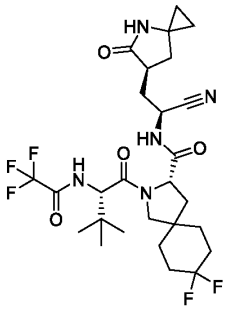
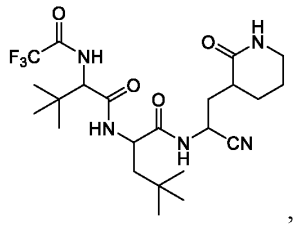
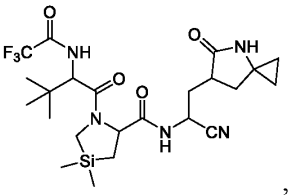
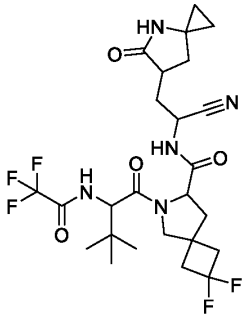
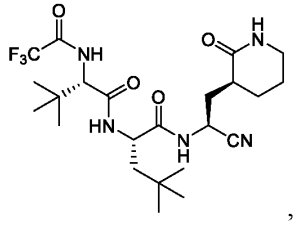
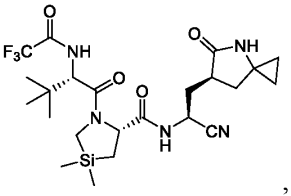
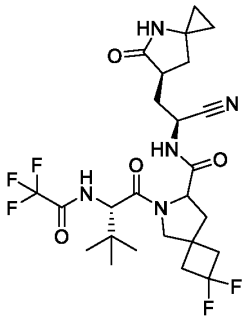
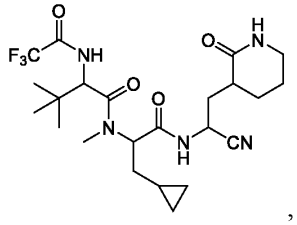
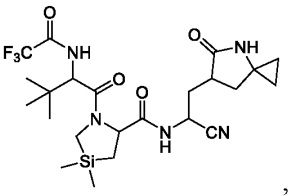


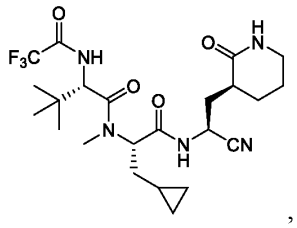
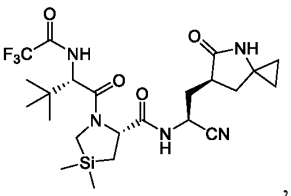
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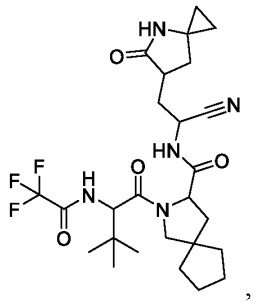
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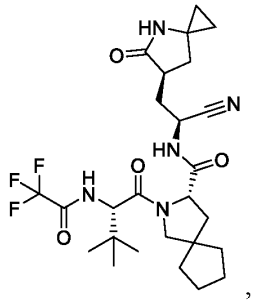

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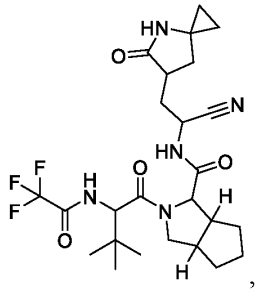

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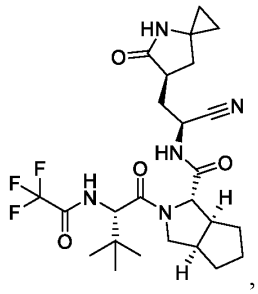
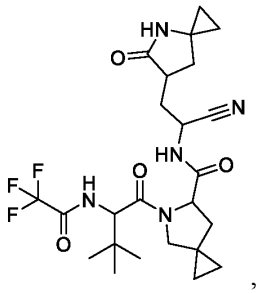
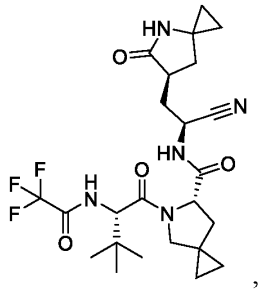
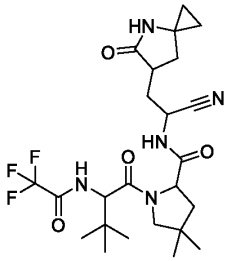
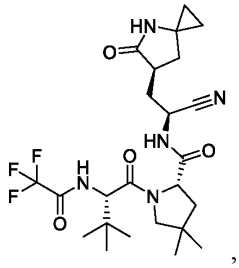
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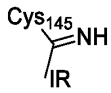

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and a pharmaceutically acceptable salt or stereoisomer thereof.

27. A pharmaceutical composition comprising a compound of any one of claims 1-26 and a pharmaceutically acceptable excipient.

28. A substantially reversible conjugate represented by:



Formula III,

wherein Cys_{145} is cysteine at position 145 or equivalent active site cysteine on a CL or 3CL protease; IR is a viral protease inhibitor; and wherein the compound that forms the conjugate comprises a -CN warhead.

29. A method of ameliorating or treating a viral infection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-26.

30. The method of claim 29, wherein the viral infection is from a virus selected from the group consisting of an RNA virus, a DNA virus, a coronavirus, a papillomavirus, a pneumovirus, a picornavirus, an influenza virus, an adenovirus, a cytomegalovirus, a polyomavirus, a poxvirus, a flavivirus, an alphavirus, an ebola virus, a morbillivirus, an enterovirus, an orthopneumovirus, a lentivirus, arenavirus, a herpes virus, and a hepatovirus.
31. The method of claim 29, wherein the viral infection is from a virus selected from the group consisting of Norwalk virus, feline calicivirus, MD145, murine norovirus, vesicular exanthema of swine virus, rabbit hemorrhagic disease virus, enterovirus (EV)-68 virus, EV-71 virus, poliovirus, coxsackievirus, foot-and-mouth disease virus, hepatitis A, porcine teschovirus, rhinovirus, human coronavirus, transmissible gastroenteritis virus, murine hepatitis virus, bovine coronavirus, feline infectious peritonitis virus, and severe acute respiratory syndrome coronavirus.
32. The method of any one of claims 29-31, wherein the viral infection is a coronavirus infection.
33. The method of any one of claims 29-32, wherein the viral infection is a coronavirus selected from the group consisting of: 229E alpha coronavirus, NL63 alpha coronavirus, OC43 beta coronavirus, HKU1 beta coronavirus, Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and SARS-CoV-2 (COVID-19).
34. The method of any one of claims 29-33, wherein the viral infection is SARS-CoV-2.
35. The method of claim 29 or 30, wherein the viral infection is an arenavirus infection.
36. The method of claim 35, wherein the arenavirus is selected from the group consisting of: Junin virus, Lassa virus, Lujo virus, Machupo virus, and Sabia virus.
37. The method of claim 29 or 30, wherein the viral infection is an influenza infection.
38. The method of claim 37, wherein the influenza is influenza H1N1, H3N2 or H5N1.
39. A method of inhibiting transmission of a virus, a method of inhibiting viral replication, a method of minimizing expression of viral proteins, or a method of inhibiting virus release, comprising administering a therapeutically effective amount of a compound of any one of claims 1-26 to a patient suffering from the virus, and/or contacting an effective amount of a compound of any one of 1-26 with a virally infected cell.

40. The method of any one of claims 29-39, further comprising administering another therapeutic.
41. The method of any one of claims 29-39, further comprising administering an additional anti-viral therapeutic.
42. The method of claim 41, wherein the anti-viral therapeutic is selected from the group consisting of ribavirin, favipiravir, ST-193, oseltamivir, zanamivir, peramivir, danoprevir, ritonavir, remdesivir, cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR- 576, and zalcitabine.
43. The method of claim 40, wherein the another therapeutic is selected from the group consisting of protease inhibitors, fusion inhibitors, M2 proton channel blockers, polymerase inhibitors, 6- endonuclease inhibitors, neuraminidase inhibitors, reverse transcriptase inhibitor, aciclovir, acyclovir, protease inhibitors, arbidol, atazanavir, atripla, boceprevir, cidofovir, combivir, darunavir, docosanol, edoxudine, entry inhibitors, entecavir, famciclovir, fomivirsen, fosamprenavir, foscarnet, fosfonet, ganciclovir, ibacitabine, immunovir, idoxuridine, imiquimod, inosine, integrase inhibitor, interferons, lopinavir, loviride, moroxydine, nexavir, nucleoside analogues, penciclovir, pleconaril, podophyllotoxin, ribavirin, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, and zodovudine.

44. The method of claim 41, wherein the additional anti-viral therapeutic is selected from the group consisting of lamivudine, an interferon alpha, a VAP anti-idiotypic antibody, enfuvirtide, amantadine, rimantadine, pleconaril, aciclovir, zidovudine, fomivirsen, a morpholino, a protease inhibitor, double-stranded RNA activated caspase oligomerizer (DRACO), rifampicin, zanamivir, oseltamivir, danoprevir, ritonavir, remdesivir,

cobicistat, elvitegravir, emtricitabine, tenofovir, tenofovir disoproxil, tenofovir alafenamide hemifumarate, abacavir, dolutegravir, efavirenz, elbasvir, ledipasvir, glecaprevir, sofosbuvir, bictegravir, dasabuvir, lamivudine, atazanavir, ombitasvir, lamivudine, stavudine, nevirapine, rilpivirine, paritaprevir, simeprevir, daclatasvir, grazoprevir, pibrentasvir, adefovir, amprenavir, ampligen, aplaviroc, anti-caprine antibody, balavir, cabotegravir, cytarabine, ecoliever, epigallocatechin gallate, etravirine, fostemsavir, gemcitabine, griffithsin, imunovir, indinavir, maraviroc, methisazone, MK-2048, nelfmavir, nevirapine, nitazoxanide, norvir, plerixafor, PRO 140, raltegravir, pyramidine, saquinavir, telbivudine, TNX-355, valacyclovir, VIR-576, and zalcitabine.

45. A method of prophylactically treating a patient at risk of viral infection, comprising administering to the patient an effective amount of a compound of any one of claims 1-26.
46. The method of claim 45, wherein the compound is administered before viral exposure.
47. The method of claim 45, wherein the compound is administered after viral exposure.

48. An engineered CL or 3CL viral protease, wherein:

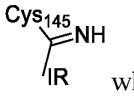
the cysteine at position 145 of the CL or 3CL protease has a non-naturally occurring covalent modification resulting from a reaction between an exogenous nitrile modifier having a nitrile function and the cysteine at position 145 of the CL or 3CL protease, and

wherein the sulfur atom at the cysteine residue and the nitrile of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein the engineered SARS- protease does not retain the protease activity of an unmodified CL or 2CL protease.

49. The engineered viral protease of claim 48, wherein the engineered viral protease substantially prevents viral replication of SARS-COV2.
50. The engineered viral protease of claim 48, wherein the CL or 3CL protease is represented by SEQ ID NO: 1.

51. The engineered viral protease of claim 48, wherein the enzymatic inhibition IC_{50} of the exogenous nitrile modifier for SEQ ID NO: 1 is less than 20 micromolar.

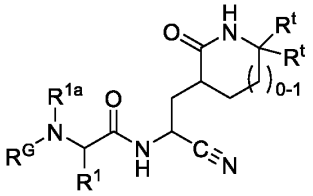
52. The engineered viral protease of claim 48, wherein the thioimidate adduct resulting from the in vivo reaction between the exogenous nitrile modifier and the cysteine at position 145 of SEQ ID NO: 1 is represented by:



wherein

IR is the exogenous nitrile modifier after undergoing the reaction.

53. An engineered SARS-COV2-3CL viral protease represented by SEQ ID NO: 1, wherein the cysteine at position 145 of SEQ ID NO: 1 has a non-naturally occurring covalent modification resulting from a reaction between an exogenous nitrile modifier, and the cysteine at position 145 of SEQ ID NO: 1, wherein the exogenous nitrile modifier is represented by:

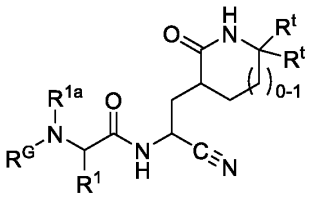


wherein the sulfur atom at the cysteine residue and the -C≡N of the exogenous nitrile modifier undergoes a reaction to form a thioimidate adduct, and wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;
R^G is –C(O)R^B;
R^B is C_1-C_6alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m, wherein R^m is selected for each occurrence from H or C_{1-3}alkyl (optionally substituted by one, two or three halo)); or a 8-10 membered bicyclic heteroaryl (optionally substituted by one, two, or three substituents each independently selected from halo or methoxy);
R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl;
R^{1a} is H; or

R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic, bicyclic or spirocyclic heterocycle optionally substituted by one or two substituents on a free carbon each selected from methyl, halo or CF_3.

54. A compound represented by:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

R^1 is C_1-C_6alkyl or -CH_2-C_{3-10}cycloalkyl;

R^G is –C(O)R^B;

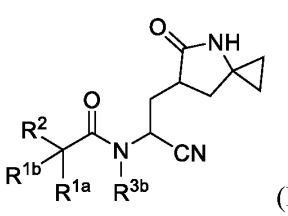
R^B is C_1-C_6alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halo, -NR^mR^m, and -NR^m(C=O)R^m, wherein R^m is selected for each occurrence from H or C_{1-3}alkyl (optionally substituted by one, two or three halo)); or a 8-10 membered bicyclic heteroaryl (optionally substituted by one, two, or three substituents each independently selected from halo or methoxy);

R^t is independently, for each occurrence, H or methyl; or each R^t may be taken, together with the carbon to which they are attached, to form a cyclopropyl;

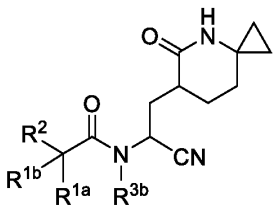
R^{1a} is H; or

R^1 and R^{1a}, taken together with the nitrogen and the carbon to which they are attached, form a 4-10 membered monocyclic, bicyclic or spirocyclic heterocycle optionally substituted by one or two substituents on a free carbon each selected from methyl, halo or CF_3.

55. A compound represented by Formula IV-A or Formula IV-B:



(IV-A) or



(IV-B)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^{1a} is selected from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –(C_1-C_8alkyl)-R^1, –(C_1-C_8alkyl)-CN, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 4-10 membered heterocycle and 5-10 membered heteroaryl;

R^{1b} is selected from hydrogen and C_1-C_8alkyl;

or R^{1a} and R^{1b} may be joined together to form, together with the carbon to which they are attached, a 4-10 membered heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl;

R^1 is selected from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle, wherein R^1 may optionally be substituted by one, two, or three substituents each selected from R^A;

R^A is independently selected for each occurrence from the group consisting of halogen, cyano, hydroxyl, oxo, SF_5, $–CH_2CF_3$, $–CF_3$, $–O-CF_3$, $–O-CHF_2$, $–S-CH_3$, $–S(O)_2-CH_3$, $–NH_2$, –O-phenyl, –O-(C_1-C_8alkyl)-phenyl, $–NHC(O)R^B$, $–NHC(O)OR^B$, $–NHC(O)O-(C_1$-C_8alkyl)-R^B, $–N(R^y)_2$, $–N(R^y)(C_1$-C_8alkyl)C(O)O-phenyl, $–N(R^y)(C_1$-C_8alkyl)$C(O)N(R^y)_2$, $–C(O)-OC(CH_3)_3$, C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_1-C_8heteroalkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, –(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), –(C_1-C_8alkyl)-(C_6-C_{14}aryl), –(C_1-C_8alkyl)-(5-10 membered heteroaryl), C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the R^B, alkyl, heterocyclyl, heteroaryl, or aryl may optionally be substituted by one, two or three substituents each independently selected from the group consisting of halogen, C_1-C_8alkyl, C_1-C_8alkoxy, SF_5, $–NH_2$, hydroxyl and oxo;

R^2 is selected from the group consisting of $–NHC(O)R^B$, $–NHC(O)OR^B$, $–NHC(O)N(R^B)_2$, $–NHC(O)C(R^C)_2R^B$, $–NHS(O)_2R^B$, –O-(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), 4-10 membered heterocycle, C_6-C_{14}aryl and 5-10 membered heteroaryl bound through the carbon or nitrogen atom, wherein R^B or R^2 may optionally be substituted by one, two, or three substituents each selected from R^x;

or R^{1a} and R^2 may be joined together to form, together with the carbon to which they are attached, a 4-10 membered mono or bicyclic heterocycle having a ring nitrogen NR^G, or a C_3-C_{10}cycloalkyl, wherein the cycloalkyl or heterocycle may optionally be substituted by one, two or three substituents on a free carbon each selected from R^A;

R^{3b} is selected from hydrogen and C_1-C_8alkyl;

R^B is independently selected, for each occurrence, from the group consisting of C_1-C_8alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_6cycloalkyl, fluorenylmethyloxy, C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

R^C is independently selected, for each occurrence, from hydrogen, halogen and C_1-C_8alkyl;

R^x is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, oxo, CF_3, SF_5, cyano, -O-(R^{xx})-OCH_3, –$OCHF_2$, –OCF_3, –O-(C_1-C_8alkyl), –C(O)O(CH_3), –N(R^y)$_2$, –N(R^y)C(O)R^y, –N(R^y)(C_1-C_8alkyl)C(O)N(R^y)$_2$, –N(R^y)(C_1-C_8alkyl)C(O)OH, -(C_1-C_8alkyl)-(C_3-C_{10}cycloalkyl), C_1-C_8alkyl, C_1-C_8alkoxy, C_3-C_{10}cycloalkyl, C_6-C_{14}aryl, -O-C_6-C_{14}aryl, 5-10 membered heteroaryl and 4-10 membered heterocycle;

wherein two geminal C_1-C_8alkyl groups, together with the carbon to which they are attached, may be joined together to form a C_3-C_6cycloalkyl optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl and oxo; and

wherein the alkyl, aryl, heterocycle or heteroaryl may optionally be substituted by one or more substituents each independently selected from oxo, halogen and C_1-C_8alkyl;

R^G is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{gg}, –C(=O)-$C_{1\text{-}6}$alkyl optionally substituted by one, two or three R^{hh}, -C(=O)-$C_{3\text{-}6}$cycloalkyl, –C(O)-(C_2-C_{10}alkenyl)-(C_6-C_{14}aryl), –C(O)-(5-10 membered heteroaryl), –C(O)-(C_1-C_6alkyl)-O-(C_6-C_{14}aryl), –C(O)-(4-10

membered heterocyclyl), and –C(O)-(4-10 membered heterocyclyloxy); wherein the aryl, heterocyclyl, or heteroaryl may optionally be substituted by one, two or three R^{ii};

R^{gg} is independently selected for each occurrence from the group consisting of -C(=O), halo, cyano, -NR^mR^m, and -$NH(C=O)R^m$;

R^{hh} is independently selected for each occurrence from the group consisting of halo, cyano, -NR^mR^m, -$NR^m(C=O)R^m$, phenyl, cycloalkyl, heterocyclyl and C_1-C_6alkoxy;

R^{ii} is independently selected for each occurrence from the group consisting of halo, oxo, hydroxyl, cyano, C_1-C_6alkyl, C_{1-6}haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_{3-6}cycloalkyl, SF_5, and NH_2;

R^m is independently selected for each occurrence from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, -$S(O)_2$-CH_3, C_{3-6}cycloalkyl, and 5-6 membered heteroaryl; wherein C_{1-3}alkyl, phenyl, and C_{3-6}cycloalkyl may optionally be substituted by one, two or three halo;

R^{xx} is –$(OCH_2CH_2)_{nn}$–, wherein nn is selected from 1, 2, 3, 4, 5 and 6; and

R^y is independently selected, for each occurrence, from the group consisting of hydrogen, C_1-C_8alkyl, C_1-C_8heteroalkyl, –CF_3, –CH_2CF_3, C_1-C_8alkoxy, –(C_1-C_8alkoxy)-(5-10 membered aryl), C_3-C_6cycloalkyl and –(C_1-C_8alkyl)COOH.